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American Heart Journal

VOL. 53 APRIL, 1957 NO. 4

Editorial

VIRUS MYOCARDITIS

MYOCARDITIS, as manifested by clinical or pathologic determinants, has been described as an occasional complication of most diseases of viral etiology. More common, however, have been reports of some transient abnormality, usually electrocardiographic, in cardiac function that has been found during the course of such infections. For neither of these circumstances has evidence been obtained that multiplication of virus occurred within any of the cells of the heart, and even the presence of the agent in the myocardium has rarely been demonstrated. Still more inconclusive is the relation of conditions classified as acute isolated myocarditis (Fiedler's) to infection by virus. Nevertheless, it is conceivable that viruses may be an important cause of heart disease, either through their direct effects on the myocardium or indirectly through substances produced by infection elsewhere in the body.

More definitive information has been contained in recent reports by Montgomery and associates,[1] in which Coxsackie Group B, Types 3 and 4, were implicated in two small outbreaks of myocarditis in infants in South Africa. Even in these cases attempts at isolation of virus from the blood stream, as well as heart muscle, might have yielded more informative results if the agent had been found in the latter site alone. In this manner, a concomitant infection with viremia could have been excluded. Similar questions arise when one considers the reports of isolation of poliomyelitis from the myocardium of patients dying from that disease. However, the probability of viral multiplication in this case is high, since the tissue tropism of the virus in cultures has been found to be extensive.

Despite the paucity of data on virus myocarditis in man, there have been ample experimental demonstrations of specific agent-disease relations in animals. Virus III in rabbits,[2] Group B, Type 3 Coxsackie in cortisone-treated mice,[3] and encephalomyocarditis,[4] in most laboratory animals have been shown to produce inflammatory lesions of the heart. In these examples intracellular inclusion bodies, recovery of virus, and demonstrable multiplication in the heart affirmed etiologic relationship to myocarditis. Undoubtedly, there are agents similarly affecting man, whether they be among the known or those yet unde-

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scribed. Cultures of human cardiac tissue should suggest the likely agents on the basis of growth and cellular damage in endothelial or muscle cells. Studies in these, as well as other types of tissue culture in which fresh postmortem material from the hearts of patients who died from viral diseases or unclassified myocarditis is employed might shed much light on etiology and incidence.

Isolation of new or known viruses in various cell cultures has now become commonplace. Such does not, however, prove etiologic relation to a clinical illness or disease in a particular organ. Extensive studies are required in which (a) the suspect agent is found repeatedly in similar circumstances, (b) infection is occurring as shown by antibody response, (c) other agents are not isolated simultaneously, (d) virus effect is present in the tissues, and (e) the illness is reproducible by infection of volunteers or preventable by vaccination of susceptible individuals. Only by careful evaluation is it possible to implicate the proper agents in human disease caused by viruses.

Another mechanism of cardiac damage must also be considered when the significance of electrocardiographic or rhythmic disturbances found in many viral diseases is under assessment. The degree of toxic symptoms in these illnesses is frequently out of proportion to the quantity of affected cells. Whether this is due to a direct toxic effect of the virus or to products of the damaged cells is not known. Experimental data are available that demonstrate direct toxicity without multiplication of influenza and Newcastle disease viruses, but there is no information on the effects of by-products of viral multiplication.

The relative importance of damage to the heart by multiplication of viruses or by indirect effect through growth elsewhere in the body obviously cannot be determined with existing knowledge. All reports indicate that recovery is complete if death does not occur during the acute phase of myocarditis associated with viral disease. If cellular regeneration occurs without fibrosis, then viral myocarditis would be of serious import only when fatal. On the other hand, if repeated scarring occurs, then the total effect over many years might be a factor in valvular or myocardial incompetence in later life.

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W. J. Mogabgab, M.D.

Original Communications

THE OUTLOOK FOR CHILDREN WITH CONGENITAL AORTIC STENOSIS

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CHICAGO, ILL.

AORTIC stenosis (valvular or subvalvular) is a fairly frequent congenital cardiac malformation. The diagnosis can be made clinically with a good degree of accuracy. All writers who discuss congenital malformations of the heart include a brief description of this entity. It is usually described as a mild condition which is well tolerated with little or no handicap. Yet almost without exception is included the sentence, "Sudden death may occur."

Curiously enough, we have found in the literature very few detailed studies of the course and prognosis of this syndrome in children. We have thought it worth while, therefore, to review all of the cases of congenital aortic stenosis seen by one of us (S. G.) during the past eight years.

This series includes eighty-five patients, all of whom were under the age of 16 years when first seen: sixty-seven boys and eighteen girls. None have a history of rheumatic infection. All have the classical signs of aortic stenosis—a loud, harsh, systolic murmur maximum in the first or second intercostal space at the right sternal border, and a thrill palpable at the same location as the murmur, or in the suprasternal notch, or both. Patients who were suspected of having congenital aortic stenosis but whose signs were not clear-cut were not included in this series; nor were any cases of doubtful etiology. No attempt has been made to distinguish clinically between valvular and subvalvular stenosis. Two of the patients had an associated patent ductus arteriosus, and three had associated coarctation of the aorta. All five were operated upon successfully for their associated lesions; and following operation, all retained the signs of aortic stenosis described above. One patient has fibrocystic disease.

The parents of all of the patients who had not been seen by us since Jan. 1, 1956, were mailed questionnaires asking them about their children's state of health and the presence of any symptoms referable to the heart. In those few cases in which the questionnaire was not returned, the patient's referring phy-

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sician was questioned concerning the patient's symptoms, if any, and his state of health. Of the eighty-five patients originally examined, we have seen fifteen since Jan. 1, 1956; and have received communications from either the parents or referring physician of an additional fifty-eight patients. Therefore, a total of seventy-three have either been seen or contacted since Jan. 1, 1956. Their present ages range from 3 months to 19½ years.

Of the above seventy-three patients, forty-one are completely asymptomatic; twenty-six have one or more symptoms; six are dead.

Before we began this survey, we were aware of only one death in this group of patients. We had seen some of these patients on repeated occasions, and they were apparently living normal, active lives. It was assumed that the others, too, were doing as well. It was, therefore, a rude shock to learn that six were dead.

The following are the case histories of those who have died.

CASE REPORTS

CASE 1.—M. C., a white boy, was seen June 21, 1954, when he was 6½ years old. He seemed able to play as hard as other children; but he had spells during which he would try to sit down and then lose consciousness. When these spells began, three years earlier, they lasted for several hours, and he remained limp throughout that time. He had had nine or ten altogether, the most recent ones lasting only ten or fifteen minutes. These spells were becoming less frequent, the patient having had only one during the year previous to his examination. His only other complaint was nose bleeds.

He was thin, with good color. His cardiac apex was felt in the fourth left intercostal space in the midclavicular line. There was a Grade 3 systolic murmur heard best in the first right intercostal space, and it gradually decreased in intensity as one moved toward the apex. A thrill was palpable over the upper sternum and in the suprasternal notch. His blood pressure was 88/66 mm. Hg, and the remainder of the physical examination was negative. The x-ray film and fluoroscopy of the chest revealed the heart to be of normal size and contour. The electrocardiogram revealed left heart strain.

On Oct. 15, 1954, while the patient was outdoors playing, he suddenly collapsed and died. He was 6¾ years old. No autopsy was performed.

CASE 2.—E. N., a white boy, was examined on Jan. 6, 1949, when he was 14 years old. He had no symptoms, and he engaged in a normal amount of physical activity although he did not participate in competitive sports. His father had a cardiac murmur and his paternal grandmother and great grandmother were also said to have had murmurs. His brother was thought to have an auricular septal defect.

The patient was well developed and well nourished. The cardiac apex was felt in the fourth left intercostal space in the midclavicular line. There was a long, loud, harsh systolic murmur best heard in the first right intercostal space. A coarse thrill was palpable in the same area and in the suprasternal notch. His blood pressure was 100/80 mm. Hg. The remainder of the physical examination was negative.

The heart, by roentgenography, was interpreted as being normal in size and contour. Fluoroscopy revealed that the left outflow tract was enlarged by elongation. The electrocardiogram revealed left heart strain.

Eight or nine months after his examination, while walking through his back yard, he suffered a syncopal attack from which he quickly recovered. He continued to engage in normal activity, including swimming and a paper route. In the summer of 1950, he was employed as a dishwasher at a Boy Scout camp. On the morning of July 15, after he had finished his work, he went swimming with a fellow employee. As he was walking through water about two feet deep, preparing to go out into deeper water, he suddenly collapsed and could not be revived. Death occurred at the age of 15½ years.

At autopsy, the left ventricle was found to be hypertrophied. There was a marked thickening of the aortic valve; the opening had a "fish-mouth" shape; and only two valve leaflets were dentifiable. The other valves were normal, and no vegetations were found.

CASE 3.—C. McK., a white boy, was seen on March 21, 1955, when he was 3½ years old. A heart murmur had been discovered when he was operated upon for pyloric stenosis, at 3 weeks of age. At the time of examination he was said to have no symptoms and to have normal exercise tolerance. However, when his mother wrote us of his death, she stated that he had not been able to keep up with other children, that he had been given extra rest, and had been carried "considerably."

He was thin, but of good color. The cardiac apex was felt in the fourth left intercostal space, in the midclavicular line. There was a Grade 3, harsh systolic murmur best heard in the second right intercostal space. A thrill was present over the upper part of the sternum and in the suprasternal notch. The physical examination was otherwise negative.

Roentgenography and fluoroscopy of the chest, as well as the electrocardiogram, were all interpreted as being within normal limits. On May 31, 1955, the patient suffered what was described as a "heart attack." On Jan. 27, 1956, the patient died of what was again called a "heart attack." An autopsy was not performed. The mother stated in a letter that before his second, and fatal, heart attack, he had awakened a few times in the night "screaming with leg-aches." He died at the age of 4 years.

CASE 4.—J. S., a white boy, was seen July 31, 1950, when he was almost 7 years old. His murmur had been discovered when he was two weeks old; and he had been kept in the hospital until he was three weeks old because, although his birth weight was six pounds and fifteen ounces, he was very listless and had lost weight. He was fed with a dropper at home; and he slowly began to gain strength. He made steady progress; and by the time he was examined, he was a fairly active boy. The mother stated that he seemed to sense what he could and could not do. Although he ate poorly and was thin, he had no complaints except that he tired a little more easily than other boys.

His chest was asymmetrical with a Harrison's groove. The lower sternal margin was prominent. The cardiac apex was felt in the fifth intercostal space, ¾ inch to the left of the midclavicular line. There was a Grade 3 systolic murmur along the right sternal margin. A thrill was felt over the whole precordium, but was particularly prominent in the suprasternal notch. The blood pressure was 84/60 mm. Hg. The remainder of the physical examination was negative. Roentgenography and fluoroscopy of the chest revealed that the heart was globular in shape and that all the chambers were enlarged. A Wolff-Parkinson-White syndrome was seen on the electrocardiogram. The P-R interval was 0.10 second, and the QRS, 0.14 second.

The patient continued to keep up fairly well with others, and had no symptoms except for tiring rather easily. Almost exactly three years after he was examined, while standing outside in the shade watching some workmen, he suddenly collapsed and died. His mother wrote that he had not been running or exerting himself in any way. He died at the age of 9¾ years. No autopsy was performed.

CASE 5.—W. G., a white boy, was examined on Jan. 5, 1948, when he was 12½ years old. A murmur was first noted when he was 3 years old, but he had never had any symptoms referable to his heart. He was very active, being able to keep up with his fellows. His only complaint was nose bleeds, which occurred about once per month.

He was found to be well developed and well nourished. The cardiac apex was seen and felt in the fifth intercostal space, 1 inch to the left of the midclavicular line. A very loud, harsh, systolic murmur was heard over the entire chest, but was maximum in the second intercostal space at the right sternal margin. A very coarse thrill was palpable in the first and second right intercostal spaces and in the suprasternal notch. The murmur was transmitted to the neck and to the peripheral vessels, being heard both in the antecubital space and in the groin. The aortic second sound was present, but was rather faint. An x-ray film of the chest indicated that the heart was slightly enlarged, being long and extending to the left. Unfortunately, the patient's electrocardiogram has been lost, but notes on his original record state that there was no axis deviation, that the T waves were inverted in Leads II and III, and that the S-T segment was depressed in Lead III.

The father of this boy wrote that he died of a "coronary occlusion" while he was playing ball, April 3, 1950, when he was 15 years old. No autopsy was performed; but the diagnosis, "coronary occlusion," was apparently assumed because of the suddenness of death.

CASE 6.—J. S., a white boy, was first admitted to the Children's Memorial Hospital on Nov. 9, 1953, when he was 2½ months old. A slight hoarseness had been noted shortly after birth, and this had become more severe during the two weeks prior to his admission. During those two weeks, he had lost his appetite and had failed to gain weight.

On physical examination, he was found to be well nourished and of good color. The cardiac apex was in the fifth intercostal space, ½ inch to the left of the midclavicular line. There was a Grade 3 systolic murmur best heard in the second and third right intercostal spaces, diminishing in intensity as one reached the apex. A faint precordial thrill was present. The femoral and radial pulsations were weakly palpable. The lungs were clear to percussion and auscultation. The tip of the spleen was palpable, but the liver edge was not felt.

An x-ray film of the chest showed that the heart was grossly enlarged; and fluoroscopy revealed that the enlargement was mainly of the left ventricle. The left auricle was also moderately enlarged. A marked left heart strain was found on the electrocardiogram.

The patient had no symptoms while he was in the hospital, and was discharged. He was readmitted on Nov. 21, 1953, because of severe vomiting, diarrhea, and dehydration. Following treatment with intravenous fluids, he recovered and was again sent home. He was home only one week when he began "wheezing." When seen by his physician, he was found to have a "very gray color," and he was admitted to another hospital. The mother saw him the next day and said he was gasping for air, even though he was in an oxygen tent. He died the following morning. An autopsy was performed at the hospital where he died, but a description of the findings has apparently been misplaced at that hospital. However, the pathologist entered the following diagnosis in the autopsy record book: congenital heart disease, aortic stenosis. The patient's age, at the time of death, was 3 months and 3 weeks.

Three of these six patients suffered at least one syncopal attack before the fatal one. Two patients tired rather easily, and were not able to keep up with their fellows. Two patients complained of nose bleeds. These were the only symptoms that any of the patients, now dead, had in common. Four had enlarged hearts, as determined by fluoroscopy and/or roentgenography, at the time they were examined. Three showed a left heart strain on the electrocardiogram; two had normal electrocardiograms; and one had the Wolff-Parkinson-White syndrome.

Of the sixty-seven patients still alive, forty-four were said by their parents to be able to compete with their contemporaries. Fourteen were able to keep up, so long as they did not engage in strenuous activity. Nine were not able to keep up. Three of the patients who were able to compete had symptoms unrelated to activity.

Among the twenty-six patients with symptoms, easy fatigability was the most common complaint, occurring in nine patients. Headaches were next in frequency, being mentioned by six of these patients. Four patients suffered spells of dizziness with exertion, and four became short of breath on exertion. (One of the latter has fibrocystic disease.) Nose bleeds occurred in four patients; and pain in the legs in three. (One of those with pain in the legs had coarctation of the aorta.) Two patients complained of spells of dizziness not associated with exertion; and the following symptoms were also reported twice: chest pain associated with exertion, faintness with extreme exertion, and syncope with extreme exertion. One patient complained of chest pain not associated

with exertion; another complained of numbness of the fingers and toes; another, of general weakness; and one, of irritability.

It is probable that some of these symptoms, such as aching of the legs, and nose bleeds, which are so common in childhood, cannot be ascribed with certainty to the patient's aortic stenosis. Three patients, in fact, who had complaints when first examined, are now reported to be asymptomatic.

Of the twenty-six patients with symptoms, five had enlarged hearts at the time they were examined. Ten showed left heart strain on the electrocardiogram; thirteen had normal electrocardiograms; two had electrocardiograms interpreted as abnormal, but showing no definite strain pattern; and one had a "borderline" record.

Many of the patients who are asymptomatic are very active. One young man, who is now 18 years old, played football during his first two years of high school. One of the two oldest patients in the series (19½ years) is a campus leader and honor student at college, and has played 36 holes of golf in one day without more than the normal tiring. The two patients who reported faintness with extreme exertion have no other symptoms and ordinarily engage actively in competitive sports.

Within the group of forty-one patients without symptoms, eleven had enlarged hearts when they were last examined. However, one of these had a patent ductus and one had coarctation of the aorta. Fourteen patients had left heart strain (one of these had a patent ductus); twenty-five had normal electrocardiograms; one had a first degree A-V block; and one had a "borderline" record.

DISCUSSION

This report of an 8.2 per cent mortality in a series of seventy-three patients under the age of 20 years is in contrast to the statement made by Lyon and Kaplan[1] in the most recent edition of Nelson's "Pediatrics," to the effect that the prognosis in congenital aortic stenosis is usually good and that symptoms usually appear for the first time during middle adult life. Nor is it in agreement with Kiloh's[2] report of twenty-seven patients between the ages of 5 and 50 with congenital aortic stenosis. In his series there were no deaths, and the eight patients with symptoms were all over 28 years of age. Campbell and Kauntze[3] reported a series of forty patients ranging in age from 3 to 50 years. There were only two deaths; these patients were 40 years of age, and both died after aortic valvulotomy. Young's[4] paper about the ten soldiers with "congenital subaortic stenosis" who performed their duties in the Army without difficulty was certainly an optimistic one, although he ended it by saying that sudden death can occur in this disease.

On the other hand, Marquis and Logan[5] reported a series of twenty-eight patients, of whom two died in infancy, two died before puberty, and one died in his teens. Two of these patients died suddenly after having had previous attacks of syncope. There were fifteen cases of congenital aortic stenosis in the series reported by Kjellberg and associates[6]; of these, five had symptoms, and one died suddenly at the age of 14. This patient had had severe symptoms since the age of 2, and at autopsy was found to have severe subaortic stenosis.

Christian,[7] Mason and Hunter,[8] and Grishman and associates[9] have all reported death from superimposed bacterial endocarditis. This threat, of course, is not so great as it was formerly.

Although it is perfectly clear that many of these patients can lead normal lives for many years, the 8.2 per cent mortality found in this study makes it just as clear that this is not an innocent disease, and that some of these children should be selected for surgical correction of their defect as soon as such a procedure is proved relatively safe. The reports published during the past two years on the results of aortic valvulotomy performed via the transventricular route have been quite optimistic (Muller and Hyman,[10] Marquis and Logan[5]). The most recent report, by Bailey and associates,[11] states that the authors have operated upon nine children with congenital aortic stenosis, with no deaths. They do not state how many of these children were improved; but among their sixty-eight patients (the majority with rheumatic aortic stenosis) operated upon by the transventricular approach, twenty-nine of the thirty-five survivors (and all of the children survived) were improved.

Probably all patients who have had an attack of syncope, for which no cause except aortic stenosis can be determined, should be operated upon. (The ominous importance of syncope was first stressed by Marvin and Sullivan,[12,13] in 1935, although the cases they reported were thought to be of rheumatic or arteriosclerotic etiology.) This symptom, along with easy fatigability, is probably of more significance than enlargement of the heart or left heart strain. One of our patients (C. McK.) had a normal electrocardiogram and a normal-sized heart on roentgenography and fluoroscopy when examined on March 21, 1955. On May 31, 1955, he had an attack of syncope; and on Jan. 27, 1956, he died suddenly.

It is difficult to assess the importance of cardiac enlargement and/or left heart strain as indications for surgery. Some of the patients who are active and in apparent good health have cardiac enlargement and/or left heart strain. On the other hand, patients with a definite handicap may have neither. All of the patients who died had either symptoms, left heart strain, cardiac enlargement, two of these danger signals, or all three. It would probably be good judgment to say that any patient who is severely handicapped should be considered for surgery, whether he has x-ray and electrocardiographic changes or not. Most patients, however, with a severe handicap do already have these changes. If a patient is asymptomatic, he should be considered a surgical candidate if either his x-ray or electrocardiographic changes are marked. To note progressive changes in symptoms or of cardiac size and strain, these patients should be examined at least once a year. The asymptomatic patient with normal roentgenogram and electrocardiogram can probably be given a good prognosis; but he, too, should be checked frequently.

It may be that with further surgical advance the mere presence of congenital aortic stenosis will be regarded as an indication for surgery.

Bailey and associates[11] have recommended left heart catheterization prior to aortic valvulotomy. We have had no personal experience with this pro-

cedure, but considering the fact that it should be performed on a nonanesthetized patient to give valid results, it would hardly seem feasible in many of these children.

Perhaps none of these patients should engage in competitive sports; but it would not seem fair or logical to further restrict those patients with no signs or symptoms. With the possible exception of the boy who was playing ball, none of the patients died while over-exerting himself. For this same reason, it does not seem fair to tell the parents of those with no signs or symptoms that sudden death may occur. They would then live in a state of constant, helpless fear.

SUMMARY

A study to determine the course and prognosis of congenital aortic stenosis in children is presented. Of the seventy-three patients on whom a follow-up study was accomplished, forty-one are asymptomatic, twenty-six have symptoms, and six are dead. Five of the six patients died suddenly; and all six were under the age of 16 years.

Although the occurrence of sudden death has been mentioned frequently by earlier writers, the 8.2 per cent mortality rate found in this series is higher than one is led to expect from most previous reports. For this reason, it would seem that selected cases should be considered for aortic valvulotomy. The principal indications for surgery, based upon this study, are the occurrence of syncope and easy fatigability, cardiac enlargement, and marked left heart strain.

We are indebted to Dr. Vernon R. DeYoung for furnishing us with information about the autopsy findings in the case of E. N.

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ADDENDUM

Since this paper was submitted, two patients not included in this report have died at the Children's Memorial Hospital from congenital aortic valvular stenosis, proved at autopsy. One, a 10-week-old white boy, died of progressive left heart failure. The other, a 14-year-old white boy, was admitted with symptoms and signs of left heart failure. His clinical condition apparently improved following digitalization, but he died suddenly two days later.

THE EFFECTS OF NONPATHOLOGIC FACTORS ON THE ELECTROCARDIOGRAM

I. Results of Observations Under Controlled Conditions

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INTRODUCTION

FOR many years it has been known that a variety of nonpathologic factors produce changes in the electrocardiogram, especially in the T waves and RS-T segments. A variety of empirical criteria have been suggested to distinguish these changes from abnormal changes. Since our own experience indicates that these criteria are in error and since we feel that a scientific approach to the problem is possible, we have undertaken a controlled study of the electrocardiographic effects of the more common nonpathologic factors which are operative in everyday life. These factors are (1) exercise, (2) the taking of food, (3) combinations of *1* and *2*, (4) smoking, (5) change in posture, (6) changes in the respiratory level.

In the present paper the results are described and compared with previously reported criteria of normality.

METHOD

Electrocardiograms were made with a four-channel direct-writer electrocardiograph and vectorcardiograms were made with an oscilloscope on a group of normal young men and women (18 to 30 years of age). Records were made in the following sequence: (1) fasting, (2) immediately after 20 deep knee bends and every three minutes for 15 minutes, (3) after breakfast and every 15 minutes for one hour, (4) after a repetition of the exercise described above, (5) after smoking one cigarette (on those subjects accustomed to smoking). On most subjects records were made with the subject sitting up as well as lying down under each of the conditions enumerated above. In addition, observations were made (under all of the conditions described above) while the subject took a deep breath (except immediately after exercise). The deep breath was held only for that period of time required to record about six heartbeats. More prolonged holding of the breath in deep inspiration has different effects. These were studied in some cases but will be dealt with separately.

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RESULTS

The Effects of Exercise.—In the normal subject exercise increases the heart rate and decreases the P-R and Q-T intervals. An increased height of the P waves, especially in Leads II and III, and a more noticeable auricular T wave frequently occur. Since the auricular T wave may continue beyond the QRS complex, this may result in a depression of the first portion of the RS-T segment. After exercise, many individuals, presumably because of a change in the respiratory mid-position, show QRS changes indicative of a change in the electrocardiographic heart position. A slight decrease in the duration of the QRS complex and a proportional decrease in the magnitude of the QRS complexes in all leads as previously reported by Siegel also occur in most subjects. Of much more importance clinically, however, are the changes which occur in the RS-T segments and T waves.

All of our normal subjects demonstrated RS-T segment and/or T-wave changes immediately after exercise. These rapidly disappeared and although some individuals showed changes three minutes after exercise, the tracings usually returned to the initial form within six minutes.

Fig. 1 shows the electrocardiograms of three normal subjects recorded before and immediately after exercise. It can be seen that in the first subject (*a*) T_I became smaller, and T_{III} which was originally negative became positive. In the second subject (*b*) all of the T waves became smaller after exercise. In the third subject (*c*) T_I became slightly smaller and T_{III} which was originally positive became deeply inverted. These examples were selected to demonstrate the different patterns of T-wave changes which were encountered in the limb leads as a result of exercise. Stated briefly the T axis swings to the right (*a*) to the left (*c*) or remains unchanged (*b*); it generally diminishes in magnitude. These tracings, except perhaps for the third set (*c*) would excite no comment even among empirical electrocardiographers. Fig. 2 shows the tracings of another normal subject. The flat to inverted T_I and the inverted T_{II} and T_{III} occurring after exercise would probably be considered pathologic by many electrocardiographers. An analysis of the T-wave changes in these four subjects will be presented later.

The exercise effects largely parallel increase in rate, but at times they persist when the rate has returned to the pre-exercise level. The importance of this observation resides in the fact that the electrocardiographic changes resulting from exercise as well as the other factors studied are similar to those produced by increased rate. In brief, when the rate increases the T waves and RS-T segment of any lead tend to change in a direction opposite to that of the main deflection of the QRS complex in that lead. However, this is not invariably true and occasionally a T-wave change in the same direction of the main deflection of the QRS complex occurs.

The precordial leads of the four subjects whose tracings are presented as Figs. 1 and 2 are not shown. Lowering of the T waves in Leads V_4, V_5, and V_6 occurred in each case. In some subjects they became inverted (Fig. 3). Many clinicians fail to observe the full magnitude of the RS-T segment and T-wave changes in the left precordial leads following exercise because these leads are

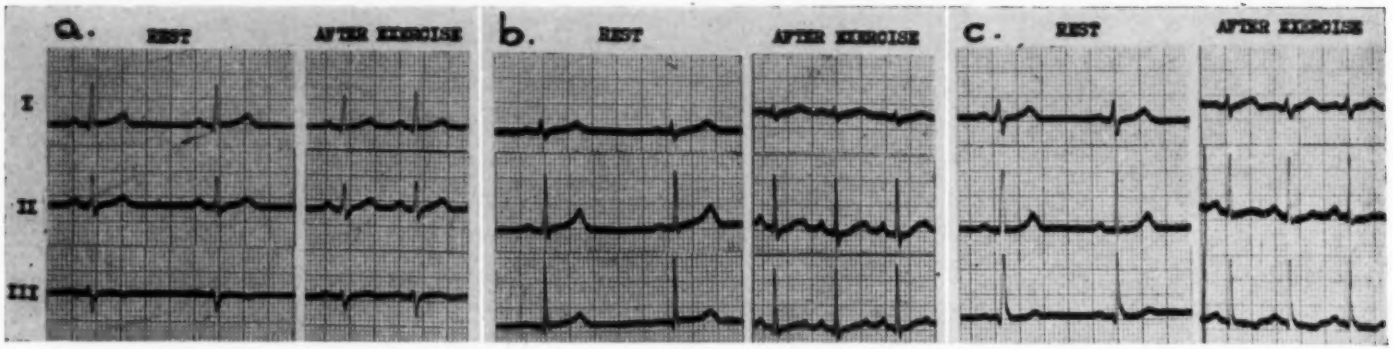


Fig. 1.

Fig. 1.—Electrocardiograms of three normal subjects before and after exercise. Note in *a* that the inverted T wave in Lead III became upright while in *c* the upright T wave in Lead III became inverted. In *b* the T waves became proportionally smaller in all three leads. Thus exercise caused the mean T vector in *a* to deviate to the right and in *c* to deviate to the left; no change in the direction of the mean T wave occurred in *b*.

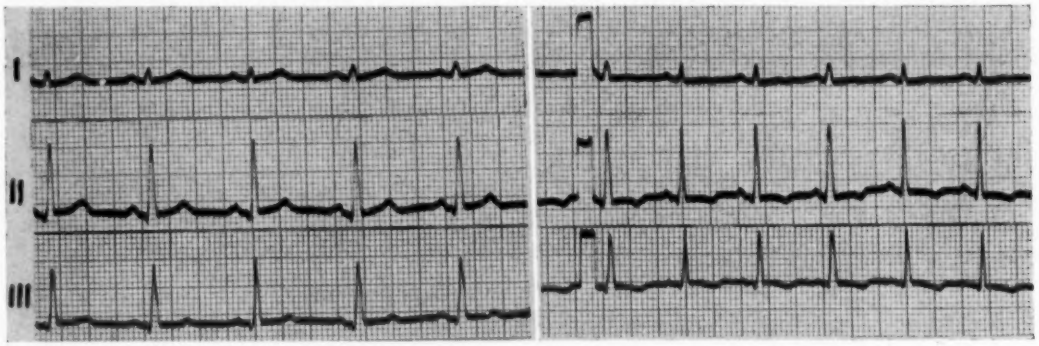


Fig. 2.

Fig. 2.—Electrocardiograms of a normal subject recorded before and immediately after exercise.

RESTING SITTING P EXERCISE IHR P C SITTING P EXERCISE SMOKING

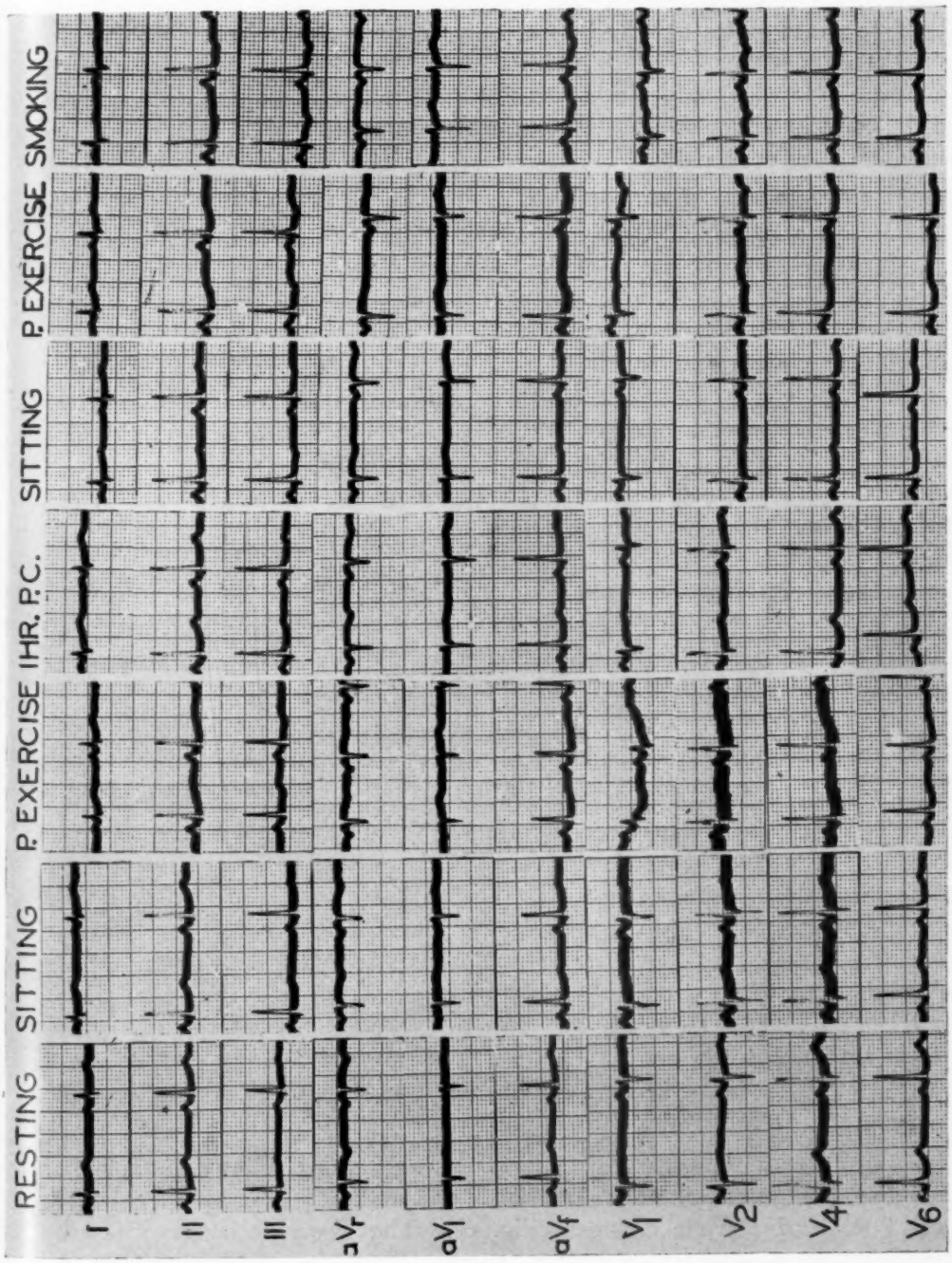


Fig. 3.—Series of observations on a normal subject. Tracings were made on subject fasting, lying flat in bed, propped up on a back rest (45 degrees), immediately after 20 deep knee bends, one hour after eating breakfast, propped up on a back rest, after the same exercise 1 hour postprandially, and after smoking one cigarette. Note the RS-T segment and T-wave changes produced by these factors.

generally recorded last and several minutes may elapse between completion of the exercise and recording of the precordial leads. If the precordial leads are recorded first, the RS-T and T-wave changes following exercise will be found to be more marked in these leads than is generally recognized.

RS-T segment shifts occurred commonly following exercise. Contrary to published reports it was found that shifts of the magnitude of 1 mm. or more were not rare. It was noted that these RS-T shifts tended to be proportionate to and opposite in direction to the main deflection of the QRS complex of the lead in which they occurred. They were also proportionate to the rate.

Effects of Food.—In most individuals an increase in heart rate occurs after a meal. Frequently the mean manifest QRS increases in magnitude and in many, as evidenced by changes in the QRS complexes, there is an important change in the electrocardiographic heart position. The most marked changes, however, are seen in the RS-T segments and T waves. These changes reach their maximum in about one hour and last from two to three and one-half hours. In any given subject they are similar to the changes which result from exercise provided no change in cardiac position or rotation occurs. In most subjects they are not as marked as the changes which result from exercise. In many normal persons no electrocardiographic changes are seen following food.

In agreement with others[1] it has been found that postprandial RS-T segment and T-wave changes are more marked following the ingestion of 100 grams of glucose than following the usual mixed meal.

Also in agreement with others[2] it was found that exercise performed 45 minutes to one hour following a meal produces more marked effect than the same exercise performed fasting.

Although increase in rate most often occurs following the taking of food, the electrocardiographic effects cannot be entirely due to rate increase for they are frequently pronounced when no increase in rate has occurred (Fig. 4).

Effects of Smoking.—The electrocardiographic changes due to smoking are more widely appreciated than those due to food. When evaluated by popular empirical criteria these changes (Figs. 3 and 5) may be regarded erroneously as pathologic. When T-wave changes occur following smoking, they are similar to those which follow exercise. Some of our subjects exhibited no changes following smoking, while in others the change was even greater than that which followed exercise. It was noted that smoking generally produced a marked increase in rate, and the effect may be in large part due to this factor. In any single subject the changes due to smoking are qualitatively similar to those due to increased rate, exercise, and food.

Effect of Postural Change.—In general, it was found that change from the supine to the sitting position (45 degree angle on the back rest in bed) frequently produces QRS and T-wave changes (Fig. 4). The T-wave changes may be very striking and are similar to those which result from exercise, food, and smoking. They may be exaggerated by having the patient take a deep breath. The QRS changes are presumably due to change in the electrocardiographic heart position.

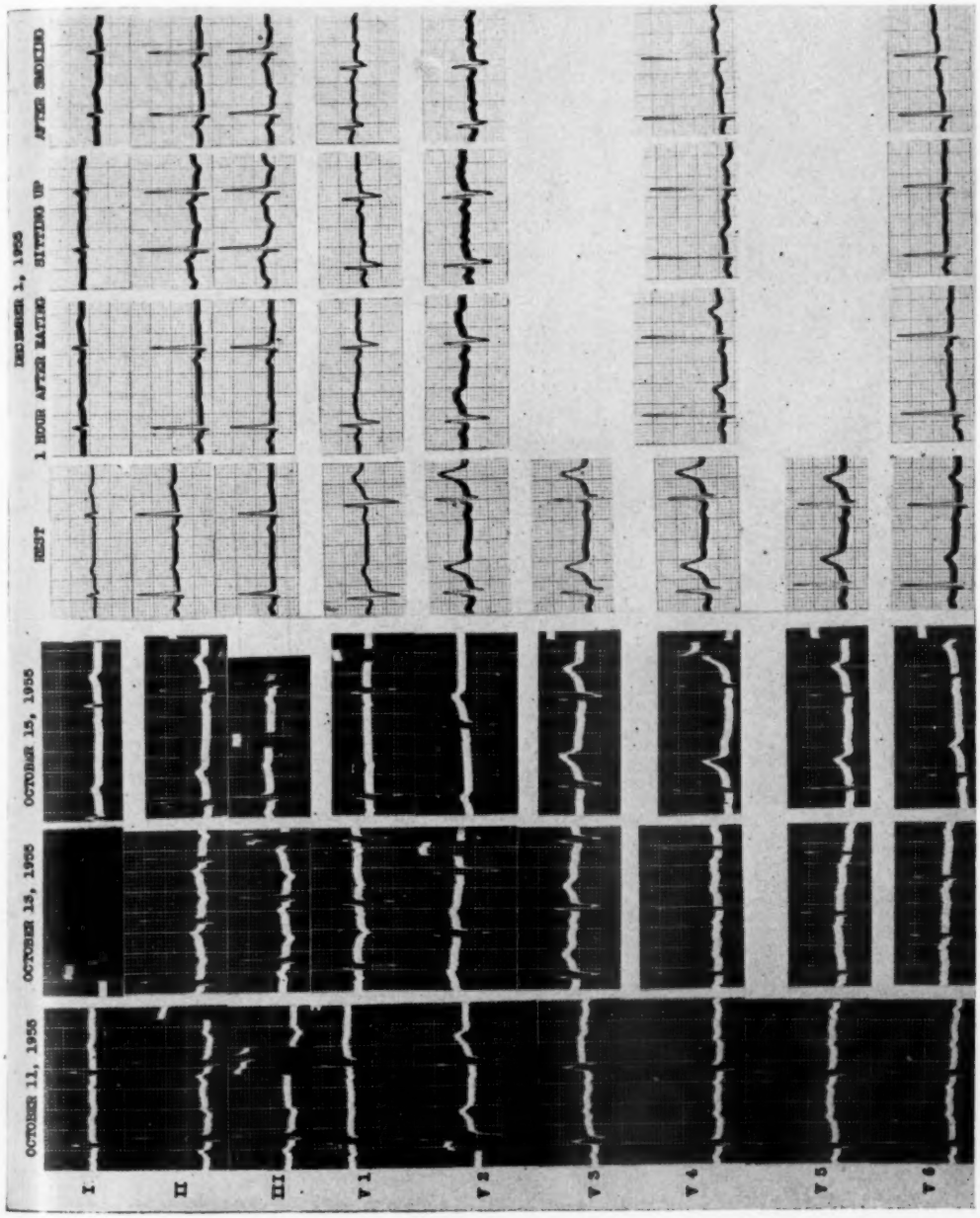


Fig. 4.—Electrocardiograms of a 27-year-old woman in whom heart disease was suspected only because of the appearance of the first two tracings which showed inversion of the T wave in Lead II and low T waves in the left precordial leads. The third tracing was recorded with the patient supine and fasting. As seen in the succeeding tracings made during a single morning the same changes that were present in the first two electrocardiograms were duplicated by the taking of food and change of posture. The last tracing was recorded with the subject supine after smoking one cigarette.

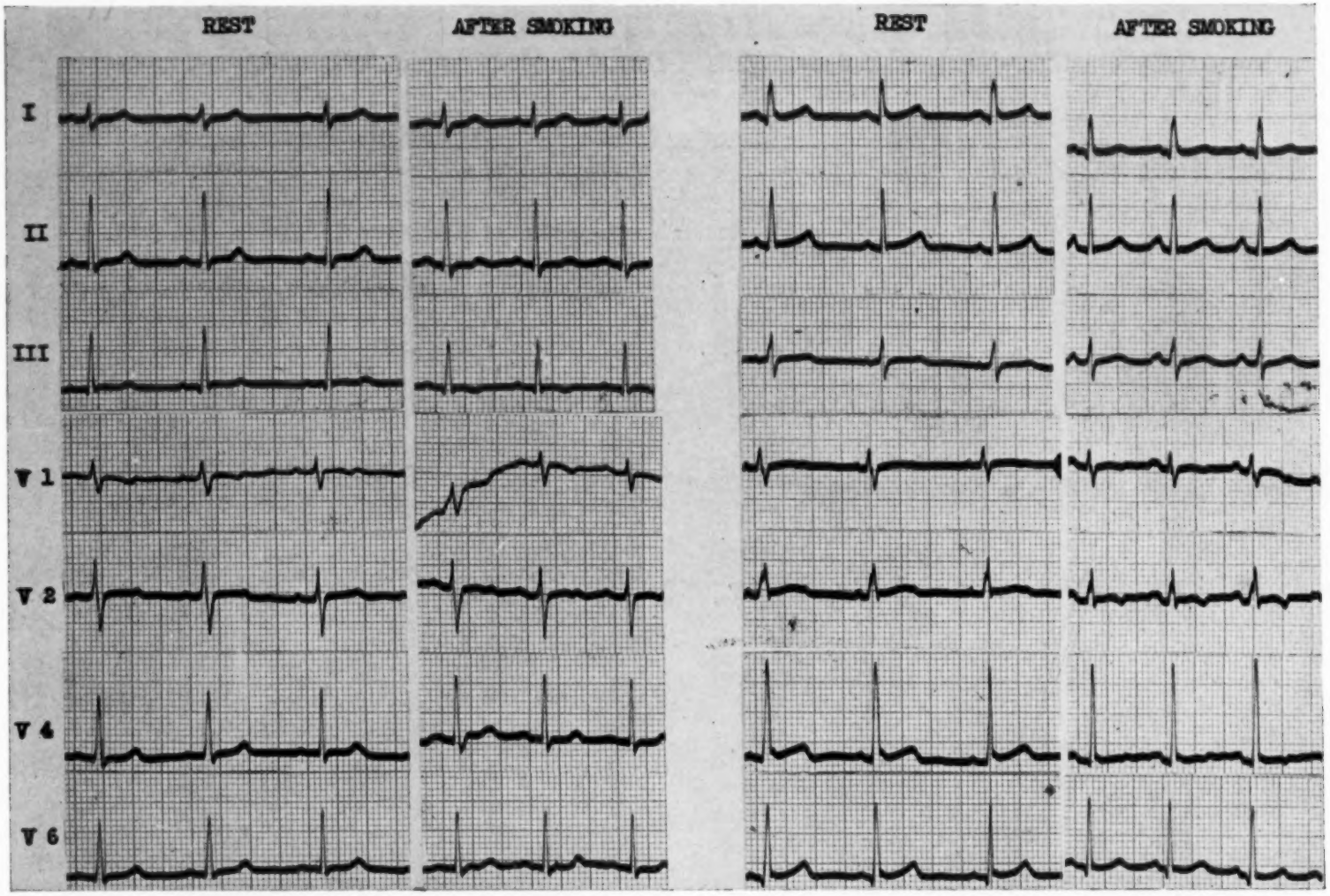
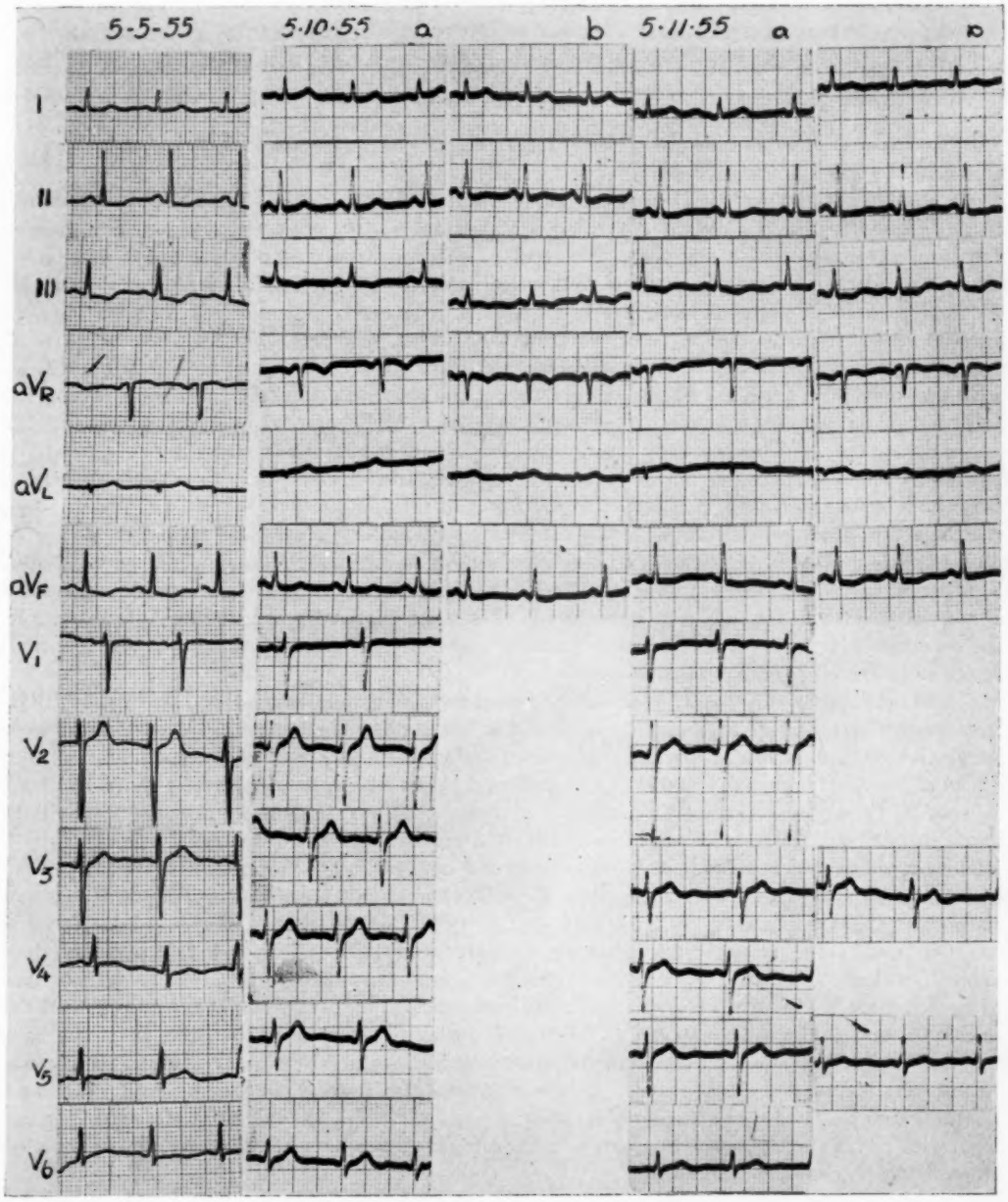


Fig. 5.—Electrocardiograms of two normal subjects made before and immediately after smoking one cigarette. Note particularly inversion of T_{III} in the first set of tracings and the effects of smoking on the T waves of the precordial leads in the second set of tracings. As pointed out in the exercise tracings in Fig. 1, the mean T-wave axis deviated to the left in the first subject and to the right in the second.

Effect of Changes in the Respiratory Level.—The QRS changes which occur during normal breathing are exaggerated when a deep breath is taken. They are well known. A detailed description of these changes is not permitted by the available space. The mean QRS usually deviated to the right. In most



A. *B.* *C.* *D.* *E.*

Fig. 6.—Effects of food and exercise on the electrocardiogram. This 18-year-old woman was suspected of having heart disease solely because of the depressed RS-T segment and inverted T waves in Lead II, III, and aV_F in tracing recorded May 5, 1955. These changes were not present in the resting tracing of May 10 (*a*); nor even after exercise (*b*). On May 11 a tracing was made one hour after a large meal (*a*) and immediately following this after 10 deep knee bends (*b*). Note the similarity between the tracings of May 5 and May 11 (*b*). Review of the history revealed that the tracing of May 5 was made, fortuitously, immediately after walking two blocks very rapidly one hour after a midday dinner.

subjects T_I becomes lower and T_{II}, and T_{III} becomes higher. The T waves in the left precordial leads may become higher, lower or remain essentially unchanged. Occasionally T_{II} and T_{III} become lower or inverted with a deep breath in the normal individual. The lowering of the T waves of the left precordial leads which may occur in the sitting position may be exaggerated by taking a deep breath. In some individuals the inverted T waves in the left precordial leads that result from exercise, etc., become upright when the subject takes a deep breath.

The clinical importance of the effects of these generally neglected nonpathologic factors may be illustrated by the following cases:

The first patient was an 18-year-old student nurse who had a brief period of syncope while on duty and because of this was seen by her physician. Other than this isolated episode she had been perfectly well in the past. Physical examination revealed no abnormalities. Laboratory procedure included the making of the electrocardiogram shown in Fig. 6,*A*. Because of the depressed RS-T segment with inverted T waves in Leads II, III and aV_F, this tracing was interpreted by others as indicative of heart disease. When seen by us the history and physical examination were not in any manner suggestive of heart disease and her electrocardiogram (Fig. 6,*B*) was normal. A review of the circumstances under which the original electrocardiogram had been made revealed that she had eaten a large lunch, and then noticing that she was late for her appointment, had walked very rapidly one block and up a flight of stairs in order to arrive on time. The electrocardiogram was made immediately after her arrival. It was felt, therefore, that the form of the tracing probably was the result of the combined effects of food and exercise, and that this conclusion could be firmly established by making a series of tracings: *B*, Fig. 6, under basal conditions; *C*, after 10 deep knee bends; *D*, one hour following a large meal; and *E*, after 10 deep knee bends following *D*. Under these circumstances the original, supposedly abnormal, electrocardiogram was reproduced. No heart disease is believed to be present and the depressed ST segments and inverted T waves of the original electrocardiogram were a normal response to exercise and the taking of food.

The second patient, the 27-year-old wife of a physician, was hospitalized on Oct. 11, 1955, because of chest pain of a pleural type. Neither her history nor a physical examination were suggestive of cardiovascular disease. As shown in Fig. 4 the electrocardiograms of Oct. 11 and 13, 1955, revealed inverted T waves in Leads II and III as well as low T waves in V_4, V_5, and V_6. In spite of these electrocardiograms it was felt that she did not have heart disease. Since both of these tracings had been recorded in the early afternoon while she was lying supported by a back rest, the technician was instructed to make the next tracing (October 15) before the patient had eaten breakfast and while lying flat. The T-wave changes previously discussed were not present at this tracing.

On Dec. 1, 1955, several weeks after her discharge from the hospital, an attempt to reproduce those T-waves changes under more controlled conditions was made (Fig. 4). It can be seen that after breakfast T_{II} became flat and T_{III} became inverted. The T-wave changes resulting from the taking of food were not so marked as those seen during her hospitalization, but when the back rest was elevated (approximately 45 degrees from the horizontal) the T-wave changes seen during her hospitalization were duplicated. It is not unusual for T-wave changes to result from such postural changes. The last tracing (Fig. 4) was made while she was lying flat after smoking one cigarette. This tracing, when compared to the one made one hour after eating, shows the electrocardiographic effects of smoking.

DISCUSSION

The primary importance of the electrocardiographic effects of rapid rate, exercise, food, smoking, and change in posture resides in the fact that electrocardiograms are generally made under uncontrolled conditions and are interpreted without regard to the possible effects of these factors. Since inversion of the T wave in certain leads, e.g., Lead II and the left precordial leads, is popularly regarded as abnormal according to empirical criteria, many tracings are called

abnormal which are actually normal. Marked changes developing in serial studies presented can easily be very misleading. We have seen many persons upon whom an erroneous diagnosis of cardiac disease has been made because of the failure to recognize that such marked T-wave changes need not be pathologic.

The distinction of the normal from the abnormal is frequently difficult and not rarely impossible, but it seems evident that no basis for judgment can be sound unless it rests upon a knowledge of what can happen in the normal. The results presented in this paper must make it obvious that the criteria employed heretofore are next to worthless, especially when they are applied to records which are not made under basal conditions. Obviously, electrocardiograms must frequently be made under other than basal conditions, but interpretation should take into account the possible effects of nonpathologic factors. In this connection it is important to note that the effects of hyperventilation[3] are similar to the effects of exercise, food, and smoking. The role of increased rate is important in most of these effects.

When tracings which were not made under basal conditions demonstrate RS-T and T-wave changes similar to those presented in this paper, an attempt to reproduce these changes under controlled conditions is extremely important in the clinical evaluation of the electrocardiographic findings.

In some cases no final conclusions can be reached until, as described for Case 2, studies are made of the effects of the various factors enumerated above. Even then one must keep in mind that failure to demonstrate pathologic electrocardiographic changes does not rule out heart disease.

Exercise electrocardiograms are frequently employed as a test for coronary disease and, therefore, some discussion of the effects of exercise in relation to these tests is warranted. An excellent review of this subject has been presented by Scherf and Schaffer.[4] This paper reviews the various empirical criteria which had been published up to 1952. We are in agreement with these authors in their evaluation of the previously published criteria. However, in view of our own findings we must disagree with the statement that "any shift of the T vector after exercise, to the extent that a distinctly inverted T in any or all of Leads I, II, V_4, V_5, and V_6, is definitely pathologic." As may be seen in Figs. 1, 2, and 3 exercise may cause inversion of the T wave in any one or in several of these leads. Frank inversion of the T wave in Lead I is unusual following the exercises usually employed in tests for coronary insufficiency.

Various criteria for distinguishing normal from abnormal RS-T shifts have been published. Considerable controversy revolves about the magnitude of the RS-T "depression" which may be considered normal in some particular lead or combination of leads. Almost without exception the various authors fail to relate the RS-T shifts to the direction or magnitude of the QRS complex. Our findings are in general agreement with those of Ashman[5,6] who showed that RS-T shifts which result from nonpathologic factors tend to be opposite in direction to, and proportionate in magnitude to, the main deflection of the QRS complex in the lead in which it occurs. Empirically we might agree with the statement of Scherf and Schaffer that RS-T depressions larger than 2 mm. are likely to be abnormal. However, it must be emphasized that in any lead the magnitude and direction of the RS-T shift which is permissible depends upon the direction

and magnitude of the QRS complex. If the QRS complex consists of a very large R wave, an RS-T "depression" of 2 mm. may be normal, whereas an RS-T "depression" of half this magnitude should excite suspicion if it follows a small R wave. On the other hand, if an RS-T shift which is induced by exercise is in the same direction as the main deflection of the QRS complex (a "depression" of the RS-T following QRS complex consisting of a small R and a large S, or an "elevation" of the RS-T segment following a QRS complex consisting of an R wave) it is almost invariably abnormal. Normal RS-T elevations following QRS complexes which consist largely of R waves in any lead almost uniformally become smaller after exercise. However, it is to be remembered that RS-T shifts due to injury may also diminish or disappear after exercise. A detailed discussion of RS-T segment shifts will be presented in a subsequent paper.

Since the effects of exercise one hour following a meal are greater than those which occur when the exercise is performed three to four hours after a meal or fasting on the same day, it is possible to obtain considerably different results in two exercise tests performed on different dates. Thus, if the food factor and other nonpathologic factors are ignored, it is possible to draw erroneous conclusions regarding the coronary circulation.

Up to this point we have discussed the T wave following increased rate, exercise, food, smoking, and postural changes as empirical phenomena. Certainly, viewed in this manner no order is detectable in the assembled data. As stated earlier, the only general description which can be made is that as observed in the limb leads the frontal plane T axis may deviate to the right or to the left or it may remain the same. There is hardly any other change that it can undergo. It was stated that the T axis generally becomes smaller, but it can occasionally become larger. This chaotic state can be resolved only through an analysis of T-wave potentials upon a physiologic basis. A subsequent paper will attempt to demonstrate that the concept of the ventricular gradient must be employed if order is to be brought to this area of electrocardiography.

SUMMARY

A study of the electrocardiographic effect of nonpathologic factors (exercise the ingestion of food, smoking, changes in posture, and deep breath) has been made in a group of healthy young persons.

The necessity for recognition of the effects of these factors in the interpretation of electrocardiograms is emphasized.

The necessity for revision of the criteria selected by previous writers in the evaluation of the exercise electrocardiogram is illustrated and discussed.

It is suggested that only a physiologic approach can result in a better understanding of the effects of these nonpathologic factors.

We wish to acknowledge the help of Dr. Richard Ashman in the preparation of this paper.

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THE EXPERIMENTAL PRODUCTION OF CORONARY ARTERY INSUFFICIENCY AND OCCLUSION

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AN EXPERIMENTAL means of producing chronic occlusion of the coronary arteries of the heart has been sought ever since the effects of ligation or embolism were observed about the middle of the nineteenth century.[2,8,9,15,19] The practical value of producing coronary artery occlusion in the experimental animal today is far removed from the realm of many antiquated controversies of the anatomist and pathologist of that time regarding anatomic distribution and collateral circulation of the coronary vasculature.

The active surgical approach to the therapy of coronary artery insufficiency has created an ever-increasing demand for true experimental objectivity in testing the efficacy of the multitude of myocardial revascularization procedures now in existence.[1,3,10,14,18,25-27] Most of the attempts at myocardial revascularization have been done on normal hearts followed in days to weeks by ligation of one or more of the main coronary arteries in order to test the efficiency of the extracardiac source of blood supply. These procedures have been termed supervascularization,[22] and may not be expected to offer a valid attempt at revascularization. It has been the purpose of the authors to produce areas of severe ischemia in order that a significant vascular pressure differential would exist between the grafted source of blood supply and the area to be revascularized. It has not only been assumed that the production of a true myocardial ischemia would aid in testing the validity of revascularizations, but might also tend to clarify many perplexing problems in the refinement of certain revascularizing techniques. Creation of realistic myocardial ischemia might also aid in substantiating the theory that the development of capillaries into moderate-sized arterial collateral channels is dependent on pressure relationships.[20]

Many methods have been used previously for producing infarcts in dog hearts, but most articles in the literature give inadequate statistics regarding early and late mortality and extent of infarction. One of the most popular methods is acute ligation of the anterior descending branch of the left coronary artery at its origin some weeks after the revascularization procedure. Hahn and Beck[11] reported a consistent operative mortality of 70 per cent in their

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control animals undergoing acute ligation of the anterior descending ramus in normal hearts. Significant doubt has arisen more recently concerning the applicability of these results to fulfill all experimental criteria.[7]

In 1940, Burchell[6] reported his results with occlusion of coronary vessels by various means and over different periods of time which could not be well controlled due to lack of suitable mechanisms for properly occluding these vessels qualitatively and quantitatively. It is also significant to note that radiographs of these specimens injected with radiopaque material reveal the occluding device to be located at varying distances from the coronary ostia.

Concomitantly, recent techniques in the study of early myocardial ischemia have provided insight into the possibility of future studies regarding the complex metabolic and enzymatic adjustments of the myocardium to a reduction in its blood supply.[5,13,29] Furthermore, the etiology and pace of coronary artery sclerosis are factors which remain obscure, though it is thought that they are determined by metabolic or endocrine actions. It is conceivable that the ultimate solution to the treatment of coronary artery insufficiency will lie within the realm of medical therapy. An impetus to the continued experimentation and modification with the left internal mammary artery as a means of myocardial revascularization in this laboratory has been prompted by the ominous statistics of mortality and morbidity from coronary artery disease and the present inadequacies of medical management.

An evaluation of previous experiments on coronary artery occlusions suggests that the experimental animal should survive chronic deprivation of coronary blood through the main channels, provided that sufficient time is allowed for the establishment of new collaterals and the functioning of existing intercoronary anastomoses.[1] If this be true, then what degree of coronary occlusion is necessary to produce fatal myocardial ischemia or necrosis and in what period of of time? Furthermore, what physical and metabolic state must the myocardium be in before it succumbs to the X amount of blood supply which renders it fatally ischemic or necrotic? Finally, can a heart which is slowly deprived of its supply of blood from the left coronary artery at its origin survive? These are but a few of the important questions which must be answered to aid us in the logical approach to the solution of the problems concerning coronary artery insufficiency.

This present project was planned with most of the foregoing propositions in mind. This paper deals with a new method of producing gradual occlusion of the two main branches of the left coronary artery where they originate and some of the effects therein produced.

MATERIALS AND METHODS

Gradual occlusion of the anterior descending and circumflex branches of the left coronary artery at their origins was produced by means of a hygroscopic material called Ameroid* which was introduced by Berman.[4] Ameroid is made of compressed casein which has been cured in formalin for purposes of hardening.[24] The results of in vitro experiments are given in Table I. All of the test forms of

*Ameroid casein plastic material is obtainable in 6 mm. and 12 mm. diameter rods from the American Plastics Corporation, Bainbridge, N. Y.

TABLE I. DIAMETERS OF CASEIN PLASTIC SLEEVES IN NORMAL SALINE 38° C.

	CASEIN PLASTIC BAR*	CASEIN PLASTIC SLEEVE		
	o.d.—6 mm. Length—10 mm.	uncoated† i.d.—3 mm. o.d.—6 mm. o.d. with S.S. sleeve—8 mm. length—5 mm. slot in plastic—0.5 mm. slot in S.S. sleeve—1 mm.	Glycerin coat (Same dimensions)	Petrolatum coat (Same dimensions)
DAYS	o.d. (mm.)	i.d. (mm.)	i.d. (mm.)	i.d. (mm.)
0	6	3	3	3
1	6.8	2.5	3	3
2	7.0	2.4	2.5	3
3	7.2	2.4	2.5	2.8
4	7.2	1.98	2.4	2.7
5	7.2	1.9	2.3	2.6
6	7.3	1.98	2.2	2.6
7	7.8	1.98	2.2	2.52
8	7.8	1.98	2.2	2.50
9	7.8	1.85	2.0	2.50
10	7.8	1.80	2.0	2.50
11	7.8	1.7	2.0	2.40
12	7.8	1.7	1.98	2.40
13	8.0	1.68	1.90	2.3
14	8.0	1.66	1.85	2.3
15	8.0	1.66	1.80	2.2
16	8.0	1.66	1.80	2.2
17	8.0	1.63	1.75	2.2
18	8.0	1.62	1.70	2.15
19	8.0	1.60	1.70	2.1
20	8.1	1.58	1.65	2.05
21	8.1	1.57	1.60	2.05
22	8.1	1.57	1.55	2.03
23	8.1	1.57		
24	8.2	1.5		
25	8.2	1.5		
26	8.2	1.5		
27	8.2	1.5		
28	8.2	1.45		
29	8.2	1.45		
30	8.2	1.43		
31	8.2	1.40	(In progress)	(In progress)
32	8.2	1.38		
33	8.2	1.37		
34	8.2	1.36		
35	8.2	1.35		
36	8.2	1.34		
37	8.2	1.34		
38	8.2	1.32		
39	8.2	1.30		
40	8.2	1.30		
41–50	Same	Same		

o.d. = outside diameter. i.d. = inside diameter. S.S. = stainless steel housing.
*Stock bar used in experiment to determine rate of expansion.
†Used in the experimental animal.

casein plastic were immersed in a solution of physiologic saline constantly, at a temperature of 38° C. Results given in Table I are average figures computed from values obtained from three or four test groups of casein plastic sleeves. From results derived of this in vitro experiment, it was decided to use casein plastic sleeves with an external diameter of 6 mm. and a length of 5 mm. It was necessary to encase the casein plastic in a stainless steel sleeve of at least 1 mm. thickness in order to contain the expansile force of the material and direct it toward the lumen. All lumina were cut 3 mm. in diameter. A 0.5 mm. longitudinal slot was cut in the sleeve to facilitate slipping it over the artery as it was momentarily flattened and tensed. A 1 mm. slot was cut in the stainless steel sleeve to coincide with the casein plastic. In testing further prolongations of the saline absorption of casein plastic and its subsequent expansion, other sleeves were dipped in glycerin (U.S.P.) or white petrolatum (U.S.P.). The petrolatum was

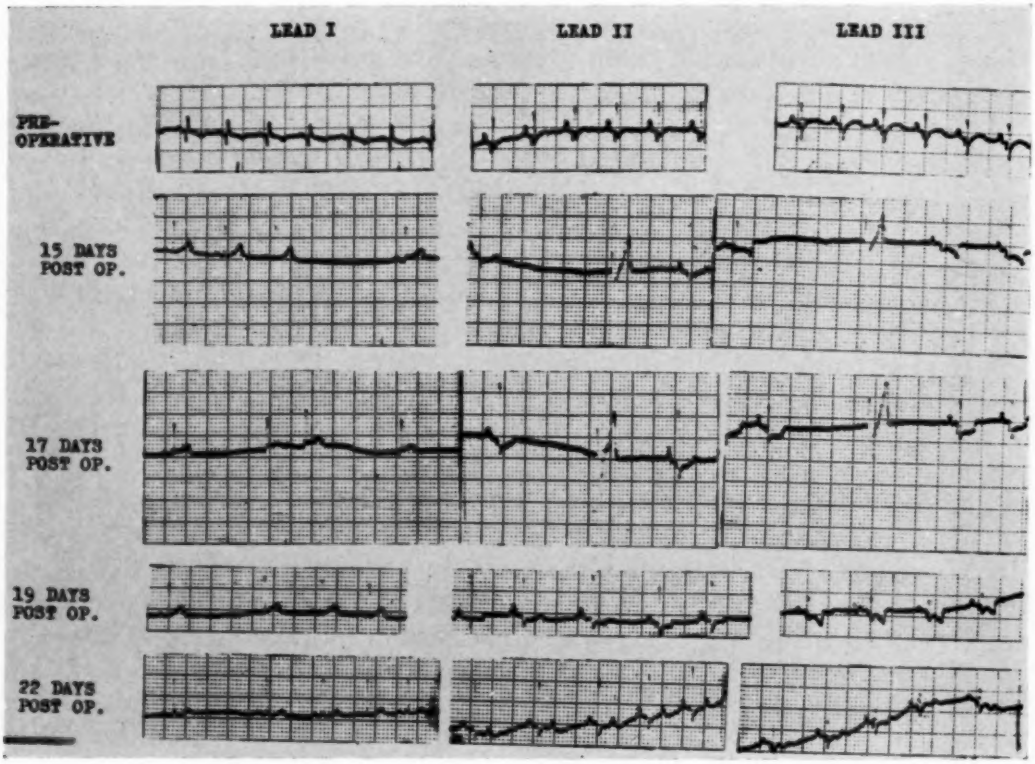


Fig. 1.—Dog 496-103. Control and serial standard limb lead ECG's. (Discussion in text.)

temporarily changed to the liquid state in a warm water bath, and the casein plastic sleeves were dipped in one or the other solution for one hour each, then lightly tapped against a table top to remove any excess solution. The results of all in vitro experiments are given in Table I, although only the plain casein plastic sleeves were used in the animal experimentation presented herein.[17]

Technique of Applying Casein Plastic Sleeves to Coronary Vessels.—Immediately prior to commencement of the surgical procedure, the casein plastic sleeves were immersed in a 1:1,000 solution of benzalkonium chloride, U.S.P., for a period of one to two hours for purposes of sterilization.

Mongrel dogs were used in these experiments, anesthetized with Nembutal, positioned with the left thorax uppermost, and intubated with an endotracheal tube which was connected to an intermittent positive pressure breathing apparatus after the pleura had been entered.

Control electrocardiographic tracings were done, using three standard limb leads after the animal was anesthetized and intubated. All tracings were done with the left thorax uppermost, before incision of the skin, using a Sanborn portable electrocardiograph.

The thorax was approached through the left sixth intercostal space. The pericardium was incised anterior to the left phrenic nerve from the level of the great vessels to a point near the diaphragm. The heart was then delivered through this incision out of the pericardial sac. A ligature was passed through the tip of the left auricular appendage and attached to a hemostatic forcep for purposes of traction. Approximately 3 c.c. of 1 per cent procaine hydrochloride was injected under the epicardium with a 24 gauge needle over the area where

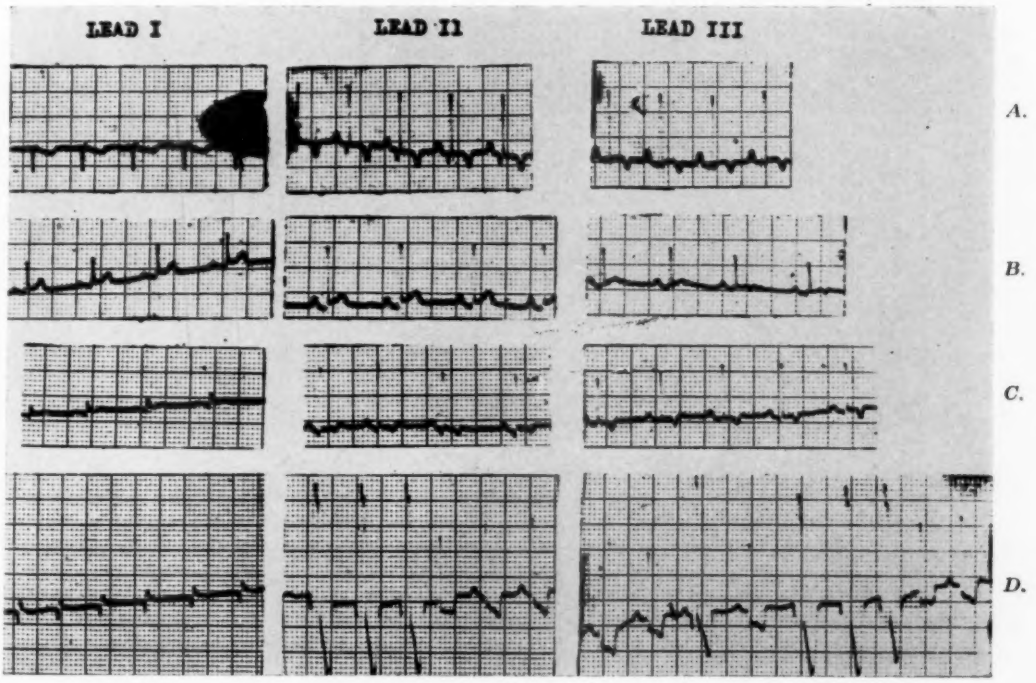


Fig. 2.—Dog 501-13. Control and serial standard limb lead ECG's. (Discussion in text.)

the left coronary artery branches into anterior descending and circumflex. A small incision was made in the epicardium overlying this area, a blunt probe inserted, and used to separate the epicardium from underlying fat and blood vessels for a distance of approximately 2 cm. down the anterior descending and circumflex branches, and then incised. The underlying coronary trunks were dissected free and all small vessels were doubly ligated with 000 plain catgut and separated proximal to the proposed areas of casein plastic sleeve application.

A loop of No. 4 linen ligature was passed around the anterior descending and circumflex branches, respectively, and utilized to maintain traction distally for a few seconds while the casein plastic sleeves were slipped on (Fig. 5). All traction ligatures were then removed, and no attempt was made to repair the

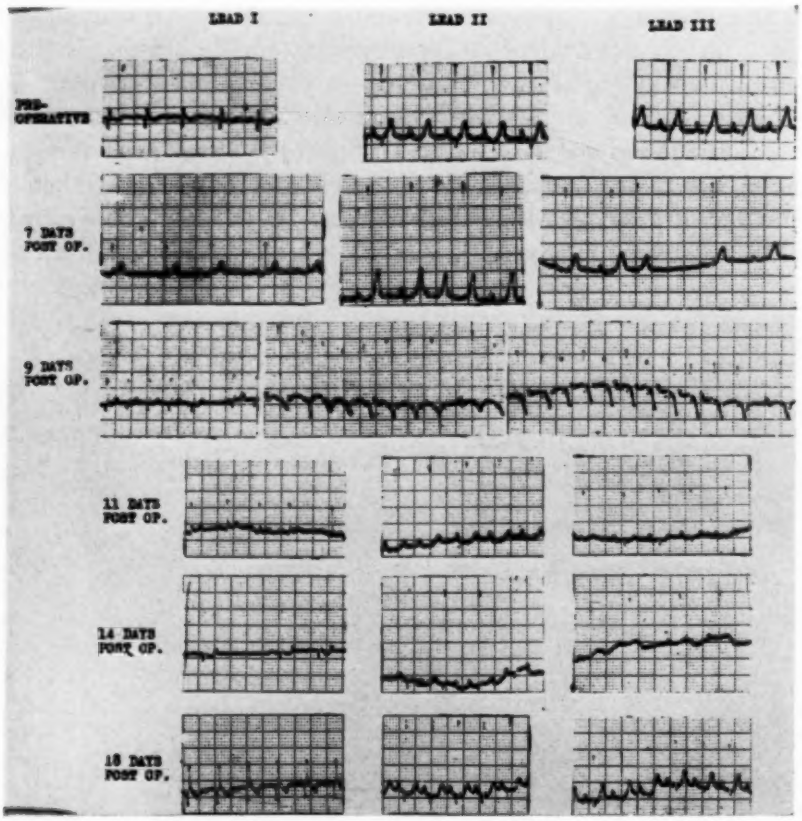


Fig. 3.—Dog 505-9. Control and serial standard limb lead ECG's. (Discussion in text.)

epicardium. The heart was replaced in the pericardial sac, and the pericardium was closed with interrupted 4-0 black silk sutures. Routine closure of the thorax was then completed after careful reinflation of the lung.

Within twelve hours after the death of each dog, a routine gross autopsy was performed. At this time, the heart was removed en masse and refrigerated in physiologic saline for twenty-four hours to allow for relaxation of muscular spasm due to rigor mortis. The hearts were then thoroughly warmed to 44° C., and the left coronary ostium cannulated with polyethylene tubing of comparable size. The tubing was attached in place by a circular ligature around the ostium and the free end attached to a Schlesinger type perfusion apparatus.[21] Injections with the Schlesinger mass was completed as outlined in the original article, and radiographs were taken to determine the degree of patency of the left coronary vessels and existence of any collateral channels.

The hearts were then preserved in 10 per cent Formalin solution, and after

78 hours were sectioned by the method described by Wartman and Saunders.[28] Each heart was sliced like a loaf of bread into sections measuring approximately 2 cm. in thickness. There were usually four uniform slices obtained from base to apex which were all placed with their superior aspect uppermost and covered

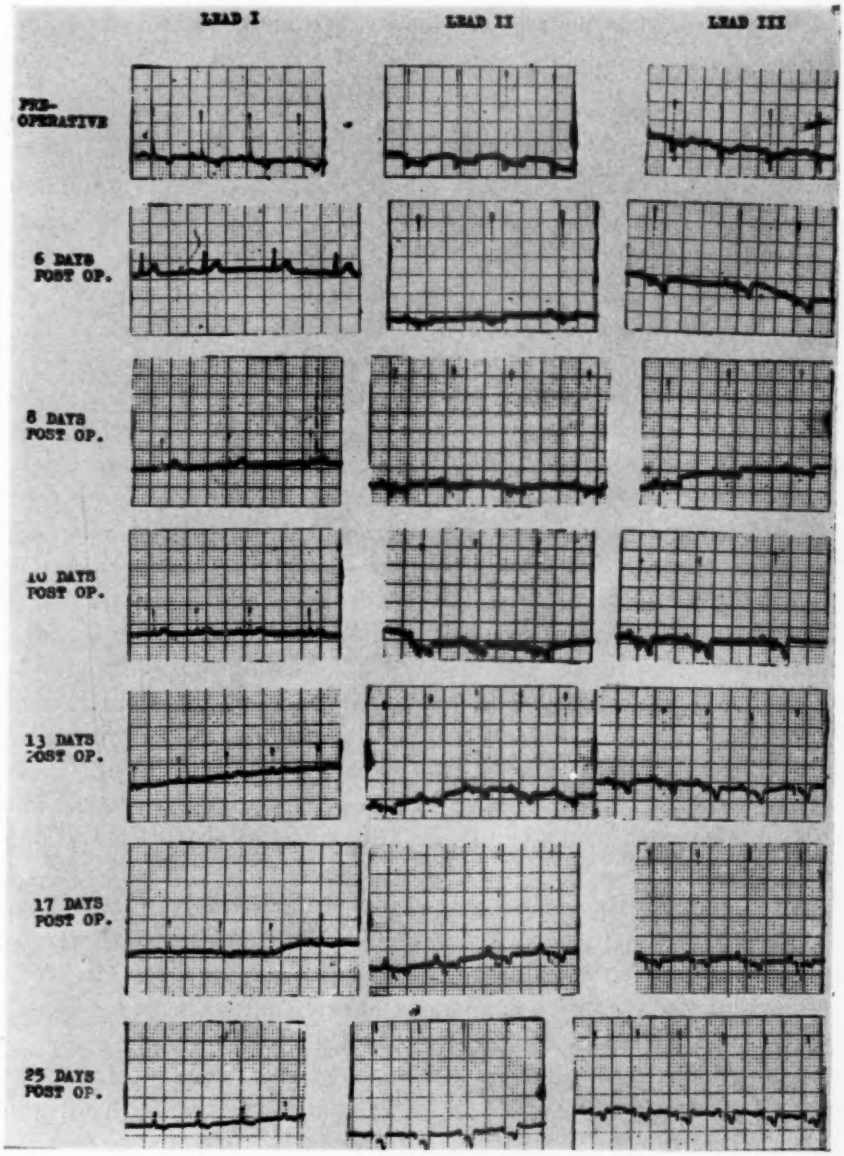


Fig. 4.—Dog 507-119. Control and serial standard limb lead ECG's. (Discussion in text.)

by a sheet of glass. Tracing paper was laid down over the glass sheet, and the myocardial outline plus grossly infarcted areas were mapped (Figs. 9 and 10). Suspicious areas of ischemia or infarction were not included, and further pathologic study of these hearts is now in progress.

RESULTS

All of the twelve dogs subjected to this procedure died within 4 to 26 days of operation.

A. *The Electrocardiographic Study.*—As previously emphasized by Horwitz, Lannek, Soave, and others,[12,16,23] the cardiogram of healthy dogs can reveal manifestations of extreme deviation. Control tracings were done on all twelve dogs preoperatively while they were anesthetized with Nembutal, intubated, and positioned with their left thorax uppermost. All postoperative tracings were performed with the dogs in the same posture, but without anesthetic or other sedatives. As evidenced by Figs. 1, 2, 3, and 4, and the other control tracings in this series, peaked and diphasic or negative P waves were noted in Leads II and III. Deep Q waves were very common in Lead I in vertical types of hearts and were occasionally seen in Lead II. T waves were mostly inverted in Lead I and sometimes inverted in all standard leads. Slight ST elevations in Lead I were observed in one control cardiograph (Dog 499-94). The rate of the normal heart varies from 100 to 160 per minute, and as a rule, sinus arrhythmia is present. Seven of the twelve dog tracings showed a neutral axis, four had a tendency to right axis, and one to a left axis deviation. These extreme variations of the canine ECG compared to its human counterpart are mainly due to positional changes. The heart of the dog lies more centrally in the thorax and assumes a more vertical position than does the human heart. The absence of much of the mediastinum compared to human beings makes the heart easily susceptible to positional changes. Consequently, pneumothorax, paralysis of the diaphragm, abdominal distention, and even variations in heart rate tend to displace and rotate the heart, producing electrocardiographic changes. Besides the positional factors, temperature variations affect the repolarization mechanism (T wave). This is very pronounced during a simple thoracotomy. The direction and the amplitude of T waves after the procedure tend to be the opposite compared with preoperative tracings. Finally, psychogenic factors, excitability, and vagal stimulation are also responsible for variations of the canine cardiogram.

Adequate postoperative ECG follow-up was carried out in four of the twelve animals operated upon (Figs. 1, 2, 3, and 4). The changes that were observed concerned mainly the alterations of the amplitude and direction of T waves, arrhythmias, and variations of the axis deviation. In all four animals, anterior wall infarcts and anterolateral extensions were detected.

Dogs 496-103, 501-13, and 505-9 all showed ECG evidence of anterior wall infarction. There were signs of anterolateral wall infarction with subendocardial ischemia in Dog 507-119. Unfortunately, due to the use of only three standard leads, more accurate localization of the necrotic, injured, and ischemic areas was not feasible. Cardiographic signs suggestive of pericarditis were noted in the first postoperative week in Dogs 501-13 and 505-9.

Arrhythmias following the myocardial changes produced by the casein plastic sleeves were quite common. They consisted of extreme sinus arrhythmia, sinoauricular block, with nodal and ventricular escape beats in Dog 496-103. The arrhythmias were more pronounced during the second and third postoper-

ative week. Periods of ventricular tachycardia with A-V dissociation and almost complete A-V block and fusion beats developed during the third postoperative week in Dog 501-13 shortly before death. It was therefore assumed that this animal died a mechanism death. Frequent auricular extrasystoles and auricular tachycardia with progressive A-V block (first degree) of the Wenckebach type was observed in Dog. 505-9.

B. *Clinical and Autopsy Observations.*—Only two of the twelve animals in this series appeared ill prior to death. The illnesses consisted mainly of asthenia, refusal to eat, drink, or move about to any great extent for one and two days before death. Most of the dogs succumbed quite suddenly, and in almost every instance, death occurred during the day while they were being exercised. (Exercise tolerances were not done.)

One dog died four days after operation, and at autopsy was found to have suffered a rupture of the left ventricular myocardium near the apex (Fig. 5).

The following is a list of the dog numbers and the days of survival after operation:

Dog Number	*Days of Survival*
504–104	4
506–126	6
499–94	11
498–199	13
501–13	15
495–193	17
494–117	
493–68	
482–105	20
505–9	25
496–103	
507–119	26

Signs of congestive heart failure were noted at autopsy in the dog dying on the eleventh day and in one on the twenty-fifth day. There were no other findings which might have suggested other abnormalities contributing to the cause of death.

C. *Schlesinger Injection Studies* (Figs. 6, 7, and 8).—Schlesinger injection was possible in eleven of the twelve hearts, and followed immediately by radiographic studies. In seven of the eleven hearts injected, both the anterior descending and circumflex branches of the left coronary artery were patent to the injection. Eight of the eleven hearts revealed patency of the anterior descending branch, and ten of the eleven circumflex vessels were open by injection.

The average luminal diameter within the casein plastic sleeves is estimated at one-fifth to two-fifths the diameter of the vessel just distal to the sleeve. There is no evidence of any collateral circulation by-passing any of these sleeves except possibly around the circumflex branch of Dog 501-13 (Fig. 7).

D. *Gross Pathologic Examinations* (Figs. 9 and 10).—Gross areas of infarction readily apparent to the naked eye were mapped in eight of the twelve

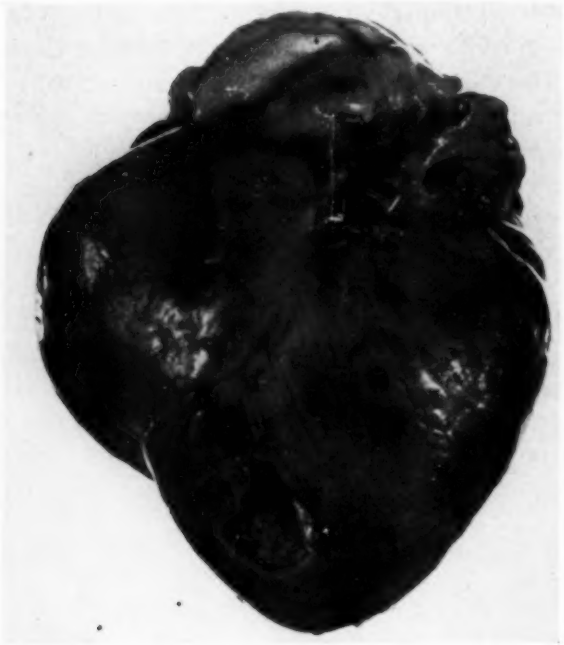
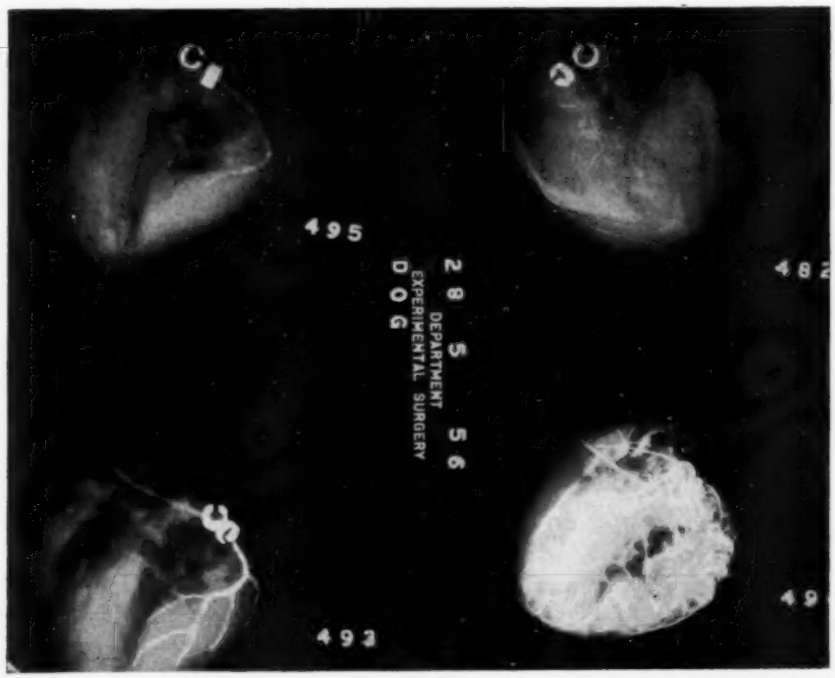


Fig. 5.—Dog 504-104. Photograph showing location of casein plastic sleeves on anterior descending and circumflex branches of the left coronary artery. Note the rupture of the left ventricular myocardium which occurred four days after application of the casein plastic sleeves.



Figs. 6, 7, and 8.—Photographs of x-rays taken following perfusion of Schlesinger solution[21] through a cannula in the left coronary ostium. (Description in text.) Dog 504-104 was not injected, due to technical failure.

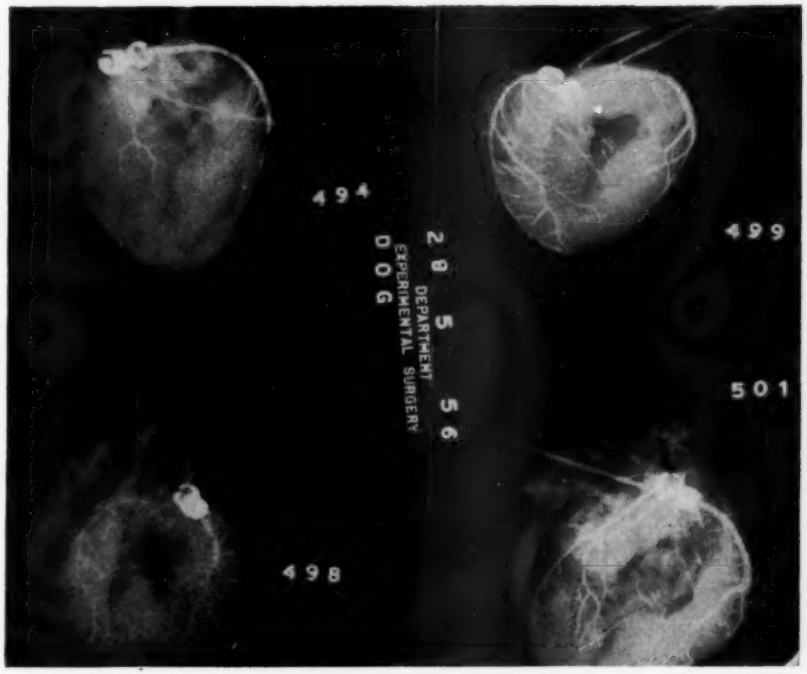


Fig. 7. *(For legend see opposite page.)*

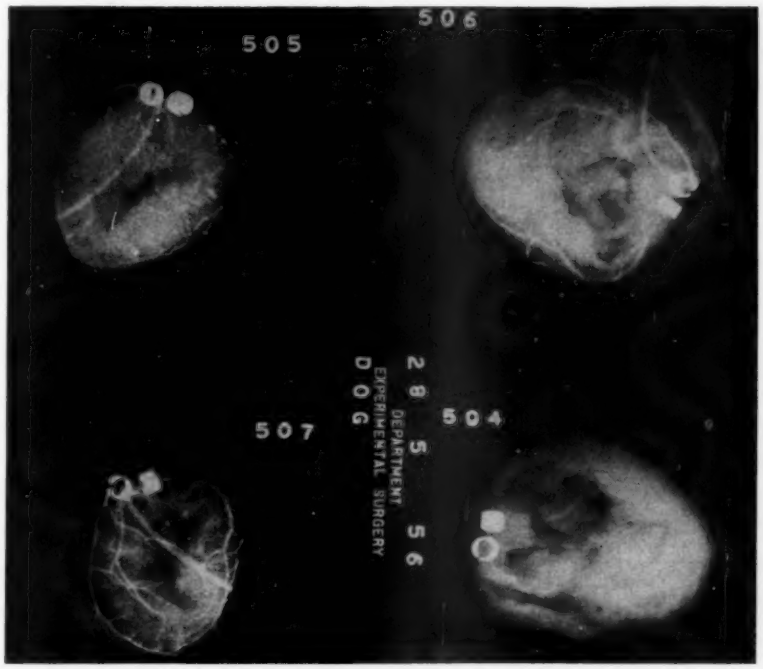
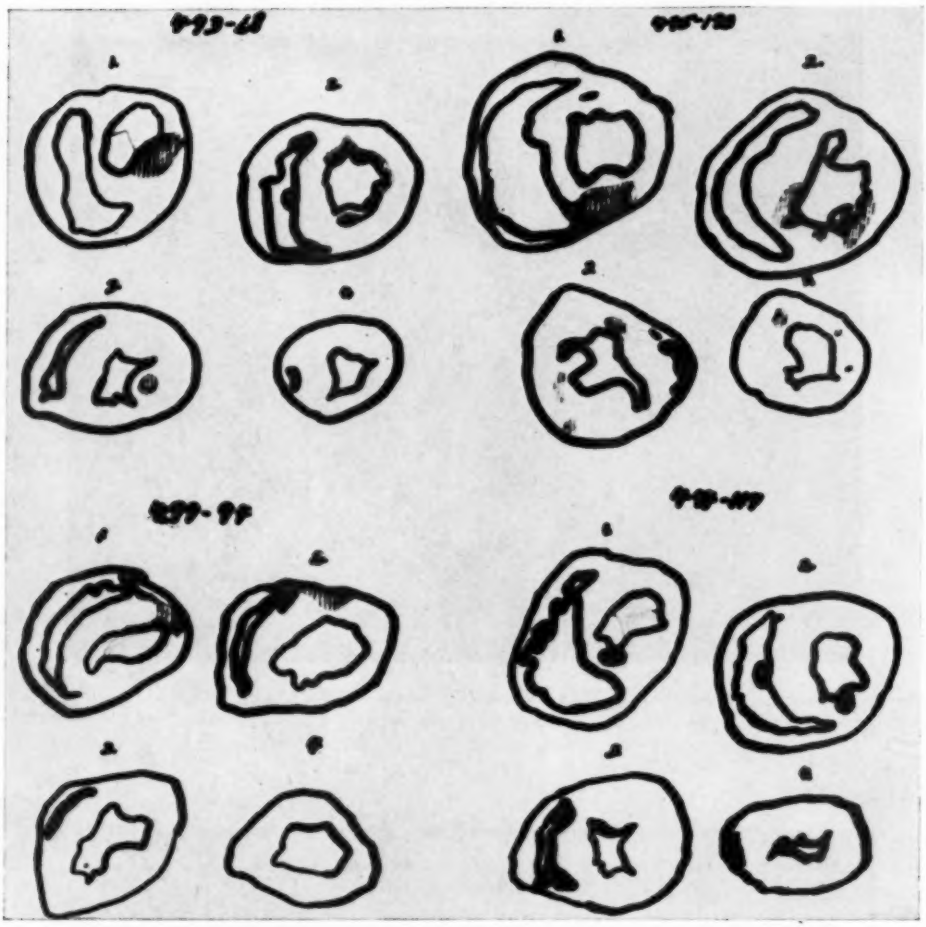


Fig. 8. *(For legend see opposite page.)*



Figs. 9 and 10.—Photographs of tracings made of heart slices after a method described by Wartman and Saunders.[28] Each slice was traced over its superior aspect, placing the anterior position in these illustrations at the bottom. Slice 1 was made at the base of each heart, and Slice 4 near the apex. Slices 2 and 3 are intermediate.

hearts (Figs. 9 and 10). Many questionable areas of infarction appeared in these eight, which are not mapped, and also in the remaining four, which are undergoing further pathologic study by histologic examination. No thromboses were evident grossly in the large coronary trunks except within and in proximity to the zone of casein plastic sleeve application. Infarcts occupy anterior and anterolateral positions in seven of the eight hearts shown in the figures. There is some septal involvement in seven of these hearts, and the posterior wall of the left ventricle is involved in four. A small amount of infarction is noted overlapping into the right ventricle anteriorly or posteriorly in three. Only three of the eight revealed gross infarcted areas extending into the apices, and the bulk of most damaged areas were at the base. Histopathologic studies of the plastic sleeve-encased vessels are to be reported on at a later date.[17]

DISCUSSION AND CONCLUSIONS

A method of gradually occluding the main branches of the left coronary artery is presented as a means of creating a more realistic type of coronary artery

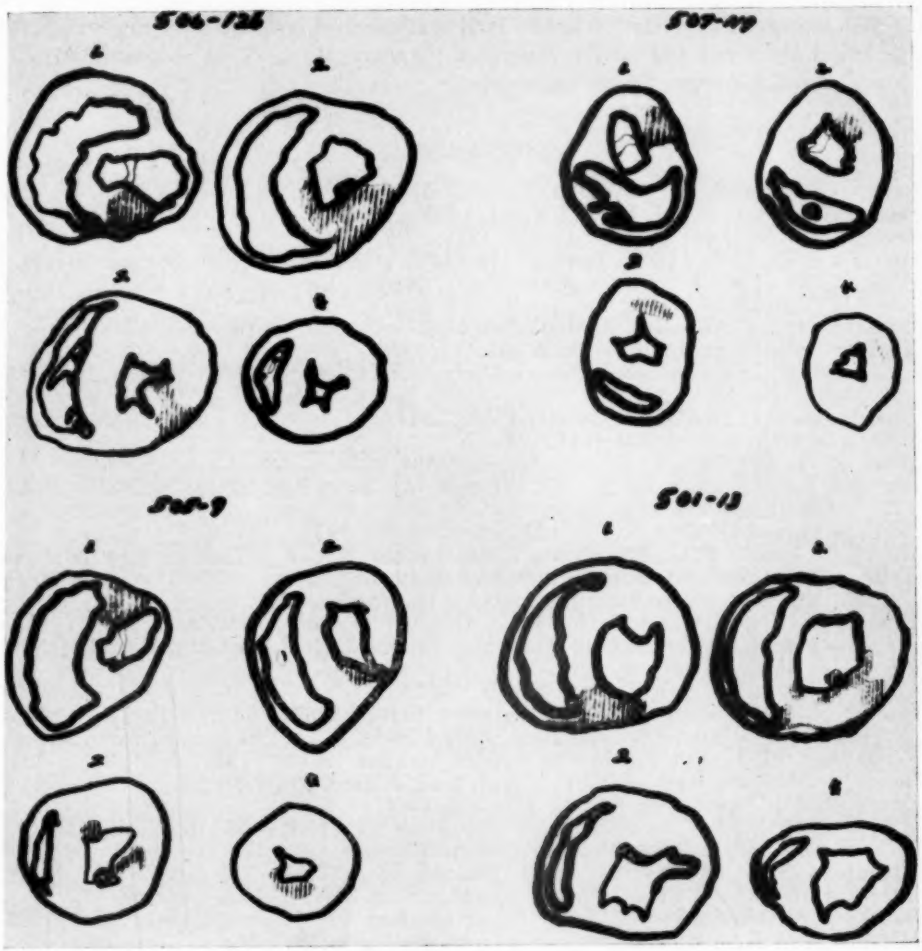


Fig. 10. (*For legend see opposite page.*)

insufficiency. The constriction of the vessels is brought about by the actual luminal expansion of the casein plastic sleeve, the fibrous tissue reaction in the tunica adventitia, and hyperplastic involvement of the medial and intimal tunicae.[17] Further in vitro tests have been done using glycerin- as well as petrolatum-coated casein plastic sleeves, proving that the rate of expansion may be slowed, as desired, for purposes of future investigation.

The serial electrocardiographic study correlates favorably with the pathoanatomic results. These findings suggest that myocardial ischemia, injury, necrosis, or derangement in the excitability and conductivity resulted from the gradual vascular occlusion. It is surmised that in most of the dogs (nine out of twelve), the occlusion was capable of producing a "mechanism" death (ventricular tachycardia, fibrillation, or asystole). In two of the others, death occurred from myocardial failure presumably and, in the last one, from rupture of the left ventricular myocardium.

It is proposed that the method of producing gradual coronary artery insufficiency, described herein, provides a more thorough and objective means of evaluating myocardial revascularization procedures.

We wish to express appreciation to Mr. Paul Roustan for his skilled operating room management, technical assistance and advice, x-ray and photographic work, as well as to Miss B. M. Macario who typed and corrected the manuscript.

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THE INTERPRETATION AND DIAGNOSTIC VALUE OF OXIMETRICALLY-RECORDED T-1824 DYE CURVES IN CONGENITAL HEART DISEASE

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DALLAS, TEX.

RECENT work has shown that the T-1824 dye curve technique, used in conjunction with cardiac catheterization, is a valuable tool in the differential diagnosis of intracardiac and aortic-pulmonary shunts. The diagnostic value of the technique lies in the fact that such shunts distort the morphology of the curves in a manner that is relatively specific for the two main types of shunts (right-to-left and left-to-right). The normal form of the curve is seen in Fig. 1. The curves may be recorded either by serial arterial sampling with subsequent analysis of blood samples for dye content, or by use of an oximeter which records changes in optical density as dye-containing blood arrives at the point to which it is attached.

One of the earlier observations was that of Knutson and colleagues,[1] who noted double-peaked curves with early appearance times in patients with right-to-left shunts. Subsequently, Nicholson and colleagues[2] described the general forms of oximetrically recorded dye (T-1824) curves that occur in the presence of various shunts as well as in congestive failure. Curves obtained in patients with right-to-left shunting were found characteristically to show early appearance times and some of them had double peaks. Left-to-right shunts had normal appearance times, lowered primary peaks, delayed disappearance, and marked attenuation of the recirculation peak. Congestive failure, with its increase in central blood volume (that within the chambers of the heart, pulmonary vascular bed, vena cava and great veins, and a portion of the aorta), was associated with delayed appearance time, markedly lowered primary peak, and very gradual descent to or near the base line with complete abolition of the recirculation peak.

The coexistence of both types of shunts may make interpretation of dye curves difficult, especially if some degree of congestive failure is also present. More precise analysis of the curves requires measurement of various time inter-

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vals on them, as shown in Fig. 2. Unfortunately, the symbols used to designate time intervals obtained from dye curves are confusing as they appear in the literature. Table I shows the symbols used in this laboratory, as well as those designated by investigators at the Mayo Clinic, on whose work rests most of our present knowledge of the usefulness of the dye curve technique in the differential diagnosis of congenital heart disease.

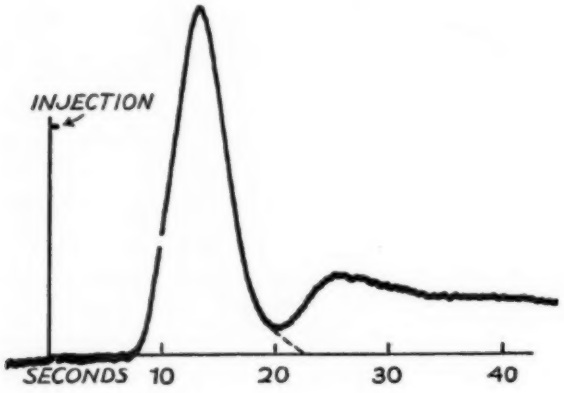

Fig. 1.—Normal oximetrically recorded dye curve.

Recently, Wiederhielm and Bruce,[4] following an earlier suggestion by Broadbent,[5] made use of certain ratios between time intervals (Fig. 2) derived from dye curves for the qualitative identification of the type of shunt present. For the identification of right-to-left shunts, a significant increase in the ratio between build-up and appearance times (BT/AT) was employed. For left-to-right shunts, an increase in the ratio between disappearance and appearance times (DT/AT) was thought to possess predictive value.

TABLE I. SYMBOLS USED FOR DYE CURVE TIME INTERVALS BY VARIOUS WORKERS

TIME INTERVAL	OUR SYMBOLS	SWAN ET AL. (1953)[10]	WOOD AND SWAN (1954)[3]
Injection	IT	IT	IT
Appearance	AT	AT	AT
Build-up	BT	BT	BT
Peak	PT	MCT	PCT
Disappearance	DT	DT	DT
Passage	DUR	PT or CT	PT
Recirculation	RT	RT	RT
Mean transit	—	—	MTT
Mean circulation	MCT	—	—
Half transit	—	—	HTT
Median circulation	MDCT	—	—

It has been established by Swan and co-workers[6] that the dye curve technique can be employed for determining the site of right-to-left shunts. The presence of double-peaked curves, with an early appearance time, at one or more injection sites within the heart or pulmonary artery, permitted localization of the defect. Dye curves have also been used successfully to estimate cardiac output and central blood volume, an application of the technique with which the present report is not concerned.

The present study was undertaken to examine the value of various time intervals and ratios in establishing the presence and type of shunts, as compared with the usual methods of identifying such shunts from blood oxygen data. As a preliminary to the above goal, the dependability of time intervals obtained from oximetric curves, as compared with those provided by direct curves, was studied, using simultaneously recorded direct and oximetric curves for the purpose.

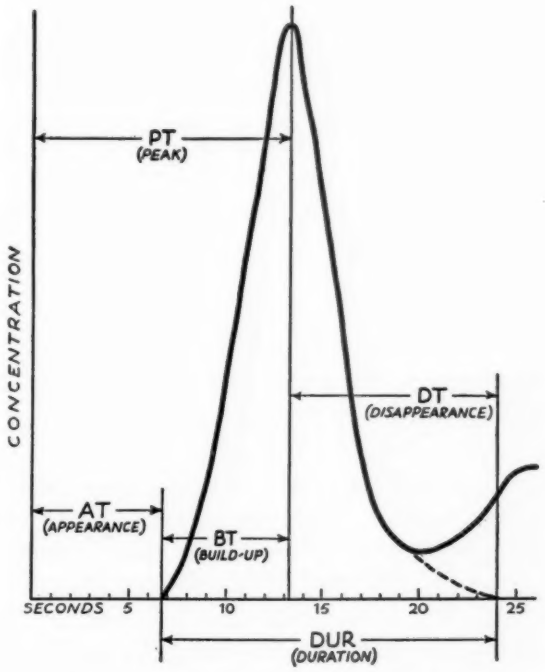

Fig. 2.—Diagrammatic curve showing points between which various time intervals are measured.

MATERIALS AND METHODS

Thirty-nine patients with congenital heart disease and 8 with congestive heart failure were studied during routine cardiac catheterization. Of the patients with congenital heart disease, 20 were less than 14 years old; the remaining 19, and all those with congestive failure, were adults. All were breathing room air at the time the observations were made.

For present purposes, patients were classified according to type of shunt by means of blood oxygen content as determined by the method of Van Slyke and Neill. Patients were assumed to have predominantly right-to-left shunts if arterial oxygen saturation was less than 93 per cent and if there was no evidence of left-to-right mixing as judged by oxygen content of blood samples taken from the right heart. If arterial saturation was less than 93 per cent and evidence of left-to-right shunting was also present, the shunt was classified as mixed. Finally, shunts were classified as predominantly left-to-right if arterial oxygen saturation was 93 per cent or higher and if blood samples from the right heart gave evidence of arteriovenous mixing.

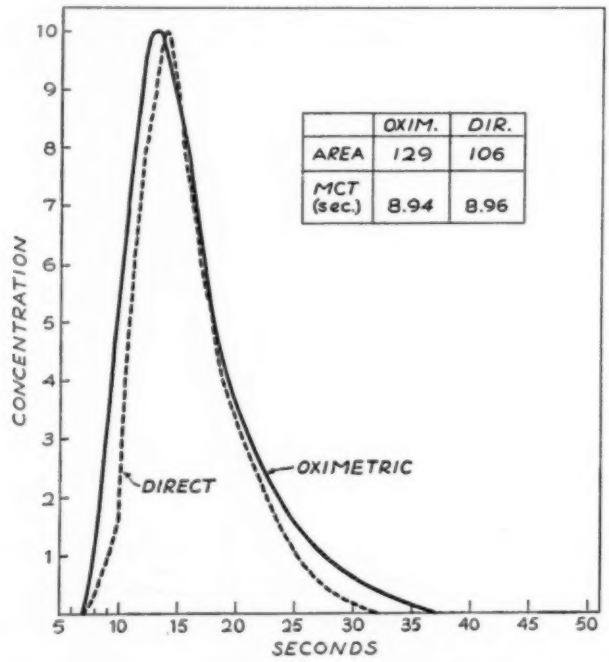

Fig. 3.—Replot of simultaneously recorded oximetric and direct dye curves in a normal adult. *MCT* refers to mean circulation time.

Patients were judged to be in cardiac failure if the right ventricular end-diastolic pressure was 6 mm. Hg, or above, and if clinical findings were consistent.

Patients in whom arterial desaturation was present but in whom there was no evidence of intracardiac shunting or shunting between aorta and pulmonary artery were excluded. The sole exception was a case in which massive pulmonary arteriovenous fistulas, easily visible by x-ray, were present.

For purposes of comparison, 17 normal subjects aged 19 to 55 years were studied. In 12 of these, simultaneous direct and oximetric dye curves were recorded, using 3 strengths of dye in each case.

Dye was routinely injected through a cardiac catheter into the right atrium. In all instances, the catheter was filled with dye solution before the test injection was carried out. A Wood-Milliken type ear oximeter, in combination with a

specially adapted breaker amplifier and an electronic photographic recorder operated at a speed of 2.5 mm. per second, was employed for registering the indirect curves. Direct curves were obtained by collecting femoral arterial blood at one-second intervals, using a mechanical collecting device.[7] Blood samples were analyzed for dye content, by use of a Beckman DU spectrophotometer.[8]

Simultaneously recorded direct and oximetric curves were replotted, using the same ordinate scales, on the assumption that the peaks of both curves corresponded to the same concentration of dye. The areas of both curves could then be compared directly. Where possible, all curves were extrapolated to zero concentration by use of the Hamilton technique,[9] an arbitrary ordinate scale being used for the oximetric curves. In the case of certain abnormal curves, notably those with markedly prolonged descending limbs and low primary peaks, extrapolation was difficult or impossible. Measurement of time intervals was carried out as shown in Fig. 2.

RESULTS

In 12 of the normal subjects comparison of areas under simultaneously determined direct and oximetric curves, replotted as described, disclosed that for the larger amounts of dye the techniques yield closely comparable results (Fig. 3). Expressing the areas as a ratio, oximetric/direct, the results were as follows:

5 mg.	1.30 ± 0.22
10 mg.	1.12 ± 0.18
15 mg.	1.06 ± 0.18

It will be noted that, when analyzed in this way, the areas under oximetric curves are usually greater than those under the direct ones, especially when small amounts of dye are injected. The reason for this systematic difference is not clear but it may have to do in part with the relatively sizable error encountered in the determination of the dye content of blood samples containing very low concentrations of dye. Appearance and peak times were also comparable as determined by the two methods. The fact that both time intervals were usually later in the direct than in the oximetric curves is largely attributable to the longer course dye must travel in the former (sampling from femoral artery) than in the latter (sampling from the ear). The results are shown in Table II.

TABLE II. APPEARANCE TIME (AT) AND PEAK TIME (PT) IN NORMAL ADULTS (IN SECONDS) AS MEASURED BY OXIMETRIC METHOD (EARPIECE) AND DIRECT TECHNIQUE (SAMPLING FROM FEMORAL ARTERY). INJECTION INTO RIGHT ATRIUM

	OXIMETRIC			DIRECT		
	5 MG.	10 MG.	15 MG.	5 MG.	10 MG.	15 MG.
AT	7.6 ± 1.3	7.4 ± 0.8	7.2 ± 0.9	10.1 ± 1.9	9.2 ± 2.1	10.1 ± 0.7
PT	14.3 ± 2.5	13.3 ± 1.3	13.9 ± 1.5	15.1 ± 2.0	14.8 ± 2.9	16.8 ± 3.5

Normal time intervals and ratios, and the data obtained from patients with cardiac disease, are set out in Table III.

TABLE III. MEAN VALUES OF TIME INTERVALS (IN SECONDS) AND RATIOS FOR NORMAL SUBJECTS AND FOR PATIENTS WITH VARIOUS SHUNTS AND CARDIAC FAILURE. INJECTION SITE: RIGHT ATRIUM

	AT	BT	PT	DT	DUR	AT/PT	BT/DUR	BT/AT	DT/AT	DT/BT
Normal (17)	7.1 ± 1.1	5.5 ± 3.8	12.6 ± 1.2	15.8 ± 4.2	21.3 ± 5.2	0.57 ±0.04	0.26 ±0.06	0.74 ±0.19	2.35 ± 0.65	2.91 ± 0.58
R—L (12)	3.9 ± 1.6	4.8 ± 1.7	8.8 ± 2.2	27.2 ± 7.0	32.6 ± 8.1	0.45 ±0.12	0.17 ±0.06	1.48 ±0.83	8.29 ± 2.35	5.46 ± 2.10
Mixed (16)	3.2 ± 1.3	6.1 ± 3.4	9.3 ± 3.5	47.6 ±35.8	52.9 ±36.9	0.37 ±0.14	0.14 ±0.06	2.24 ±1.70	11.98 ±11.75	8.56 ± 5.82
L—R (11)	6.1 ± 1.0	7.3 ± 3.8	13.4 ± 3.9	63.5 ±30.8	70.8 ±33.3	0.49 ±0.13	0.12 ±0.03	1.24 ±0.74	11.46 ± 6.12	10.12 ± 7.38
Failure (No shunts) (8)	11.6 ± 2.8	13.0 ± 5.9	24.6 ± 8.5	36.6 ±22.2	48.9 ±23.9	0.49 ±0.10	0.26 ±0.11	1.07 ±0.31	3.14 ± 1.48	3.38 ± 1.82

In defining a given value as abnormal, use was made of standard statistical conventions. If a value was within 2 standard deviations of the mean, it was considered within the normal range. Similarly, mean values were compared by calculating the standard error of the difference between them. If an observed difference between means was less than 3 times the standard error of the difference, it was not taken to be significant. In lieu of a test group of normal children, patients aged 1 to 13 years who showed predominantly left-to-right shunts were studied. In the presence of such a shunt, appearance time is usually normal (unless congestive failure is present). In this group of 10 patients, mean appearance time (AT) was 6.2 ± 1.0 seconds (as compared with 7.1 ± 1.1 seconds in normal adults).

DISCUSSION

The comparison of oximetric with direct dye curves in normal subjects shows that if 10 mg. or more of dye is injected, the oximetric technique is quantitatively reliable. The use of small amounts of dye introduces a considerable degree of uncertainty in some instances. While an instrument such as the one described above provides a wide range of amplifications and should, theoretically, render the use of small amounts of dye feasible, high amplification frequently causes unstable base lines and accentuates artefacts. In patients with shunts, cardiac failure, or arterial desaturation, this source of error becomes significant indeed, as pointed out by Nicholson and associates.[2] Fig. 4 depicts a dye curve recorded in a patient with severe arterial desaturation. Because of the high amplifications used, the oscillations in arterial oxygen saturation with the phases of respirations are very prominent. To remedy the difficulty, injection of larger amounts of dye and a lower degree of amplification are desirable. The use of pure oxygen breathing in this situation is an alternate possibility, as pointed out by Swan and associates.[10]

For the identification of right-to-left shunts, a significantly shortened appearance time appears to be as useful, or more so, than a significant increase in BT/AT. In 28 cases with venoarterial shunting (alone or combined with arteriovenous shunting) a significantly shortened appearance time (AT) was

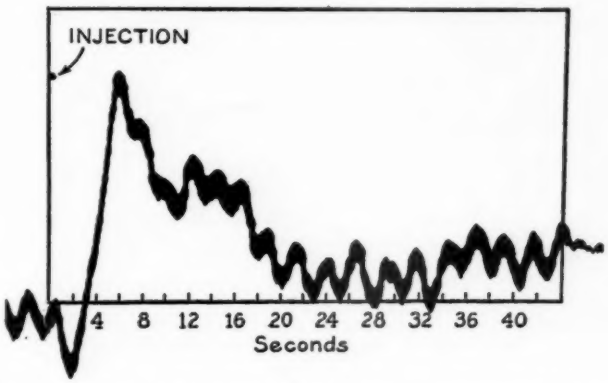

Fig. 4.—Oximetric dye curve in a patient with a large right-to-left shunt and marked arterial desaturation.

present in 24. In the same group BT/AT was significantly elevated in 19. The use of the ratio (in lieu of AT alone) therefore, serves little purpose in so far as the identification of the shunt is concerned (Table IV).

TABLE IV. SIGNIFICANT ALTERATIONS IN AT AND SEVERAL RATIOS IN TWO TYPES OF SHUNTS

	R-L (28 CASES)	L-R (11 CASES)
AT	Decreased in 24	Normal in 10
BT/AT	Increased in 19	Increased in 5 (of 10)
DT/AT	Increased in 17 (of 18)	Increased in 6 (of 7)
DT/BT	Increased in 14 (of 18)	Increased in 7 (of 7)

In some instances, where right-to-left shunting appears to take place through innumerable small vessels within the lung itself, an early appearance time does not occur, owing, probably, to the fact that the distance traveled (per unit time) by such physiologically shunted blood within the lung does not differ greatly from normal. Diffusion and distribution defects, and multiple microscopic pulmonary arteriovenous fistulas, may give rise to such conditions. Three such cases were excluded from the present study.

The presence of double-peaked curves indicates right-to-left shunting only if the appearance time of the first portion is shortened (Fig. 5). In the present material, however, recognizable double-peaked curves were the exception rather than the rule. It seems likely that, in the presence of small right-to-left shunts, the initial (secondary) portion of the curve may not be recognizable as a peak. A family of hypothetical curves, demonstrating the point, is shown in Fig. 6. The curves were constructed on the assumption that the time relations between

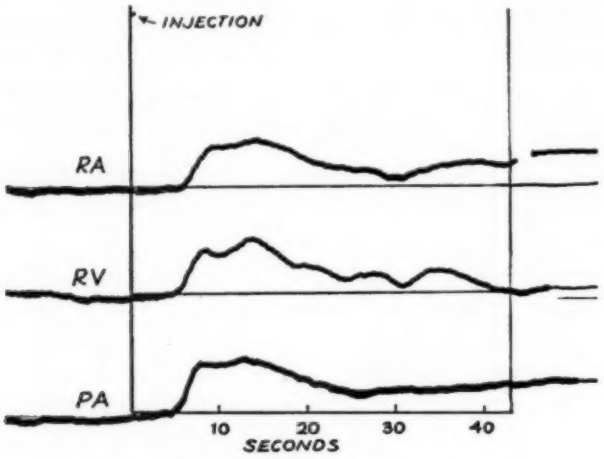

Fig. 5.—Series of double-peaked dye curves obtained in a patient with large pulmonary arteriovenous fistulas.

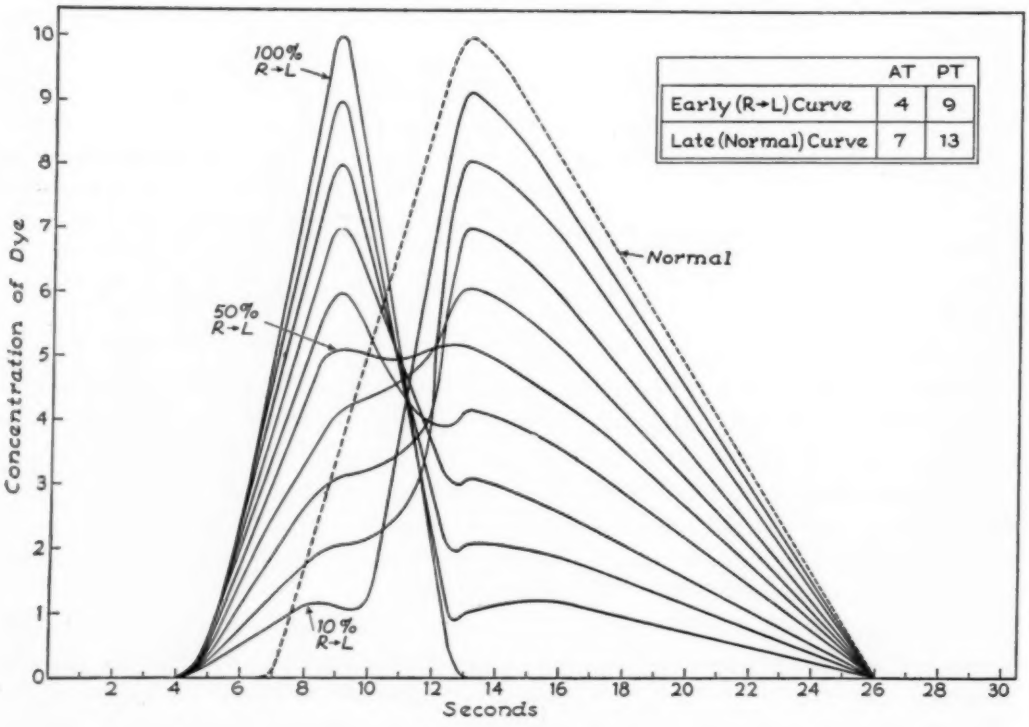

Fig. 6.—Theoretical curves representing various degrees of right-to-left shunting. Each curve is constructed on the assumption that appearance and peak times of the first and second portions (those due to venoarterial admixture, and nonshunted blood, respectively) remain constant. The assumption is also made that mixing between blood and dye is complete.

the initial and later (secondary and primary) portions of the curves do not change with alterations in the degree of right-to-left shunting. While such an assumption is almost certainly incorrect, the curves do indicate the difficulty encountered in reognizing the portions of some curves which are attributable to the abnormally early arrival of dye-containing blood at the sampling point. They also suggest that, when the right-to-left shunt is very large, the later (primary) portion of the curve, attributable to dye-containing blood that has passed through the pulmonary vessels in the normal manner, may be difficult to recognize on the descending limb of the initial (secondary) curve. Probably for these reasons, among others, right-to-left shunts do not invariably produce

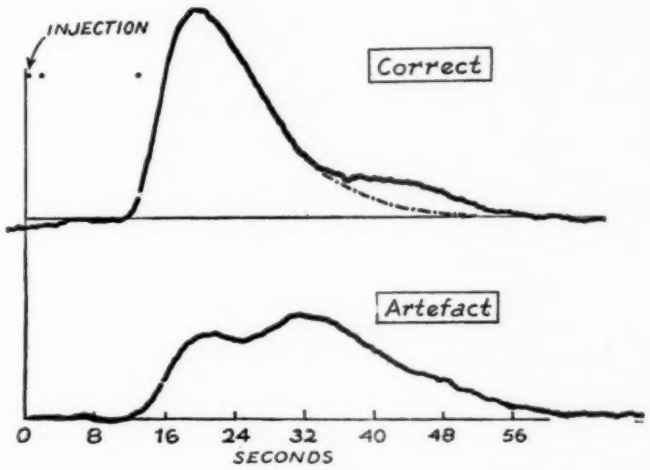

Fig. 7.—Double-peaked curve (below) produced by faulty (noncontinuous) injection of dye. The upper curve was obtained in the same patient at the same sitting when dye was injected properly.

double-peaked dye curves. The reverse also appears to be true: double-peaked curves, associated with early appearance times, occasionally occur in patients whose arterial blood is normally saturated with oxygen. Two such examples were encountered in the present study. Such curves undoubtedly indicate right-to-left shunting, presumably through the foramen ovale, at the time the dye curve is recorded. They do not, however, necessarily indicate a shunt large enough to be physiologically significant and may, in some instances, be due to placement of the catheter tip in or near the foramen. If this is the case, dye curves showing high initial (secondary) peaks in association with small right-to-left shunts may occur, since relatively undiluted dye may traverse the aperture under these circumstances. In any event, our own attempts to use double-peaked curves for calculation of the relative magnitude of such shunts in 6 patients with intracardiac venoarterial mixing have not been encouraging. Finally, double-peaked curves may be artificially created by faulty injection technique, rapid steady injection of the dye being necessary to avoid such artefacts. Such a curve is shown in Fig. 7, along with a single-peaked curve obtained in the same patient

at the same sitting. It will be noted that neither curve shows an early appearance time, a feature which serves to distinguish double-peaked curves due to faulty injection from those due to right-to-left shunting.

The present study shows the value of the serial dye curve technique, as described by Swan and associates,[6] in that it correctly indicated the site of veno-arterial shunts in 14 of the 26 cases of this type. In 6 cases results were inconclusive and, in the remaining 6, localization of the shunt had to be accomplished by other means.

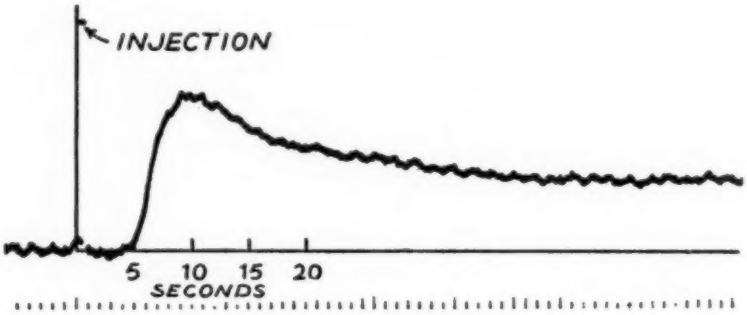

Fig. 8.—Curve representing a small right-to-left and a large left-to-right shunt in a patient with interventricular septal defect.

In the case of left-to-right shunts, no single time interval or ratio seems to possess significant predictive value (Table IV). Appearance and build-up times are ordinarily normal. Disappearance time is prolonged. In addition, peak concentrations are lower than in normal curves. Left-to-right shunt curves thus possess a characteristic morphology (Fig. 8). Any ratio that includes disappearance time should, in this situation, be altered and, for this reason, the ratio DT/AT has been used for the prediction of the presence of arteriovenous mixing. If the ratio is abnormally increased, it has been thought to be diagnostic of a left-to-right shunt. Unfortunately, the ratio is also increased in right-to-left shunts since, in the latter, appearance time (the denominator) is characteristically shortened. The ratio was elevated in 6 of 7 patients with predominantly left-to-right shunts but was also elevated in all but one of the patients with right-to-left or mixed shunts. It has, therefore, little specific predictive value. Much the same can be said of the ratio DT/BT, which has also been recommended for the identification of left-to-right shunts. A normal appearance time and a prolonged disappearance time, taken together but not combined as a ratio, offer the best means of identifying left-to-right shunts, and of distinguishing them from curves obtained in patients with cardiac failure, where appearance time is usually prolonged and the ratio normal. It would seem that significant elevation in the ratio DT/AT is good evidence that a shunt of some sort exists and that extreme elevation is suggestive, but not diagnostic, of left-to-right shunting.

In view of the valuable information that can be obtained by the dye curve technique at cardiac catheterization, it should be employed routinely as part of the procedure if the necessary apparatus is available, especially if there is reason to suspect a right-to-left shunt.

SUMMARY

Oximetrically recorded T-1824 dye curves offer a relatively reliable means of identifying the site and type of intracardiac and aortic-pulmonary shunts. The most valid indication of the presence of venoarterial admixture is a shortened appearance time (AT). Curves due to left-to-right shunts can be identified by the presence of a normal appearance time and a prolonged descending slope to which disappearance time (DT) is a good index. The use of ratios between certain time intervals obtained from the curves is of questionable value for the identification of the type of shunt present.

Double-peaked dye curves usually, but not always, indicate venoarterial admixture but are not as frequently encountered in patients with such shunts as are shortened appearance times.

Comparison of oximetric dye curves and those obtained by serial arterial sampling in normal subjects discloses that the former are quantitatively reliable both as to time intervals and as to the area enclosed, provided 10 mg. or more of dye is injected.

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KINETOCARDIOGRAPHIC FINDINGS IN AORTIC INSUFFICIENCY

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THE purpose of this communication is to present kinetocardiographic (low-frequency precordial movements) findings in patients with aortic insufficiency. Kinetocardiograms actually represent precisely defined precordial movements and impulses that are palpated routinely at the bedside. Thus the graphic definition may aid in understanding these commonly noted physical findings.

METHODS

Low-frequency precordial movements (kinetocardiograms) were recorded by means of a bellows connected to a piezoelectric transducer through an air-conduction system, previously described.[1] Pulsations were recorded from areas corresponding to the conventional precordial electrocardiographic leads and labeled KV_1, KV_2, etc. In addition, records were taken from the points of maximal apex impulses. An analysis of the patterns, as noted in normal subjects, has previously been presented.[2,3] It should be pointed out that the pattern of precordial movements may vary somewhat depending upon the reference point. Traces using this technique are absolute chest-wall movements with the reference point fixed on a crossbar outside the body. Traces made from "pickup" devices mounted on the chest wall usually record more relative intercostal space motion and may be expected to have somewhat different characteristics from the traces reported in this study and previous studies. Ballistocardiograms were taken simultaneously; however, these will not be discussed, as the technique for recording these forces has recently been changed in this laboratory, and it is apparent these tracings are not entirely reliable in that they do not give accurate representation of all forcing frequencies encountered in the ballistocardiogram. Simultaneous electrocardiograms, carotid pulses, ballistocardiograms, and kinetocardiograms were recorded on a Sanborn Poly-Viso instrument. The eighteen patients for this study were carefully selected to include only those in which the diagnosis of "pure" aortic insufficiency was reasonably certain. Table I lists the clinical data for this group of subjects, and is divided into several groups, primarily according to the functional status of the heart. This was done to facilitate subsequent discussion.

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TABLE I. CLINICAL DATA ON 18 PATIENTS WITH AORTIC INSUFFICIENCY

PATIENT	ETIOLOGY	BLOOD PRESSURE	EXERTIONAL DYSPNEA	ORTHOPNEA	PEDAL EDEMA	CONGESTIVE HEART FAILURE (LEFT)	CONGESTIVE HEART FAILURE (RIGHT)	CARDIAL ENLARGEMENT*	ECG
Group 1									
1	RHD	140/80	No	No	No	No	No	No	Normal
2	RHD	122/75	No	No	No	No	No	No	Normal
Group 2									
3	RHD	150/80	Mild	No	No	No	No	No	Normal
4	RHD	140/80	Mild	No	No	No	No	No	Normal
Group 3									
5	RHD	140/60	Mild	No	No	No	No	1+	Normal
6	RHD	130/40	Mild	No	No	No	No	2+	Normal
7	S	160/54-0	Mild	No	No	No	No	3+	Strain
8	RHD	160/60	Mild	No	No	No	No	2+	LVH
9	RHD	220/0	Mild	No	No	Mild	No	3+	LVH
10	S	155/55	Moderate	Yes	No	Moderate	No	3+	Strain
11	RHD	138/50	Moderate	Yes	No	Mild	No	2+	Strain
12	RHD	128/58	Mild	No	No	Mild	No	1+	Normal
13	S	190/40	Moderate	Yes	No	Moderate	No	2+	LVH
14	S	170/60	Moderate	Yes	Trace	Moderate	"?"	4+	LVH
15	S	140/48	Moderate	Yes	1+	Moderate	Minimal	4+	LVH
Group 4									
16	S	120/30-0	Moderate	Yes	Trace	Severe	Yes	4+	LVH
17	S	122/62	Severe	Yes	4+	Severe	Yes	4+	LVH
18	S	155/50	Severe	Yes	4+	Severe	Yes	4+	LVH

RHD = Rheumatic heart disease.
S = Syphilitic heart disease.
LVH = Left ventricular hypertrophy.
***Estimated degree of enlargement by fluoroscopic examination or a 6-foot chest x-ray.**

RESULTS

Kinetocardiographic Findings.—The kinetocardiographic records taken in the region of the lower left chest (KV_4 or region of maximal apex impulse) are the most consistent. The traces recorded from the parasternal regions, or the right side of the chest, are somewhat variable. However, if one divides the traces according to the functional classification as outlined in Table I, certain significant features become apparent; therefore, the results will be described according to the divisions presented.

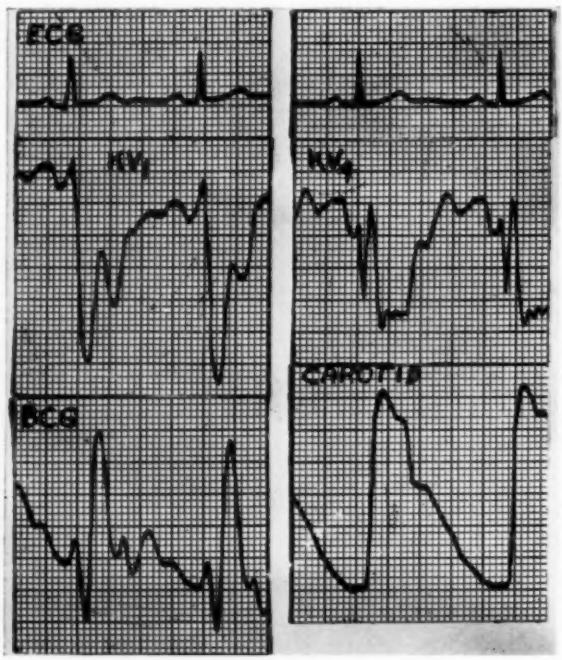

Fig. 1.—Trace taken from Patient 1 in which there was only auscultatory aortic insufficiency. This patient had no symptoms and there was no cardiac enlargement present. The electrocardiogram was within normal limits. The KV_1 trace was taken from the right parasternal region of the chest corresponding to the V-1 position of the electrocardiogram. The KV_4 trace was taken from the V-4 position which in this instance is the record from the point of maximal apex thrust. Kinetocardiograms, as well as ballistocardiograms, in this patient were within normal limits. Note that the apex thrust in the KV_4 trace begins 0.08 second after the onset of the QRS complex of the electrocardiogram. It is represented by an upward movement in the trace. It is not exaggerated in amplitude and is similar to the usual normal trace taken at the point of maximal apex thrust.

Group 1 (No cardiac enlargement, no functional impairment, no electrocardiographic changes, only auscultatory aortic insufficiency): The first two patients listed in Table I have kinetocardiograms which are essentially normal, both in configuration and time relationships. Fig. 1 is the trace from Patient 1. The apex thrust (first large upward movement after the QRS complex in the KV_4 trace) is not exaggerated over that normally noted. Thus, even in the presence of auscultatory aortic insufficiency, these two patients with otherwise normal cardiovascular systems revealed normal precordial movements.

Group 2 (Minimal symptoms only and no cardiac enlargement): Fig. 2 illustrates a tracing taken from Patient 3 in Group 2. The apex impulse is exaggerated in amplitude and the inward retraction of the apex, just preceding the apex thrust, is relatively smaller than that noted in the previous group. The traces taken from the right parasternal region of the chest (KV_1) are only slightly altered from a normal pattern. The outward movement in midsystole (which parallels the I-J upstroke in the ballistocardiogram) is exaggerated in both instances, and the late systolic movement at the time of the J-K downstroke in the ballistocardiogram is decreased.

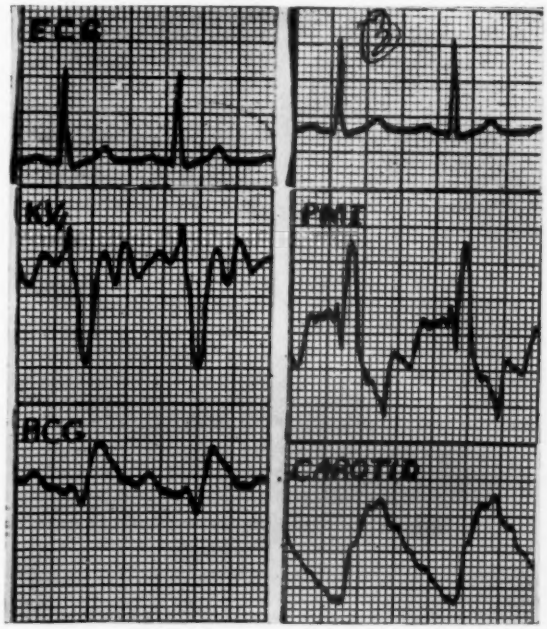

Fig. 2.—Trace taken from Patient 3. This patient was beginning to have mild symptoms of exertional dyspnea and some shortness of breath. There was no cardiac enlargement and the electrocardiogram was within normal limits. Note that the outward movement in midsystole in the KV_1 trace, which parallels the I-J upstroke in the ballistocardiogram, is exaggerated in this instance. The trace taken from point of maximal apex impulse, or in the KV_4 position, reveals an exaggerated apex thrust (outward movement beginning 0.08 second after the onset of the QRS complex in the electrocardiogram). It is the largest upward (outward) movement in the trace. Note that it terminates approximately at the time of onset of ejection as determined by the upstroke in the carotid trace. The inward movement which just precedes the apex thrust has diminished in amplitude from that usually noted and in contrast to the corresponding inward movement in the first patient (Fig. 1). Thus, as minimal symptoms develop, the exaggeration of the apex impulse is the initial change in the precordial movements, as well as a diminution in the retraction which just precedes the apex thrust.

Group 3 (Mild-to-moderate symptoms with minimal-to-moderate cardiac enlargement and electrocardiographic changes of either strain or left ventricular hypertrophy): Fig. 3 is a representative trace taken from Patient 12. There are several significant differences in these records not noted in the previous groups. The apex impulse is markedly exaggerated, beginning earlier than normal with its onset approximately 0.04 second after the onset of the QRS complex. The inward movement just preceding the apex impulses, usually noted in the apical trace, is represented only by a notch in the upstroke of the apex thrust and is

absent in many patients. The outward movement of the apex thrust terminates at the time, or very shortly after the onset, of ejection (as determined by the upstroke in the carotid pulse). The following inward motion is exaggerated, producing a marked retraction of the chest wall in midsystole and late systole. In many instances this retraction goes well below the diastolic or resting level of the chest. In addition, the normally noted outward movement, which begins

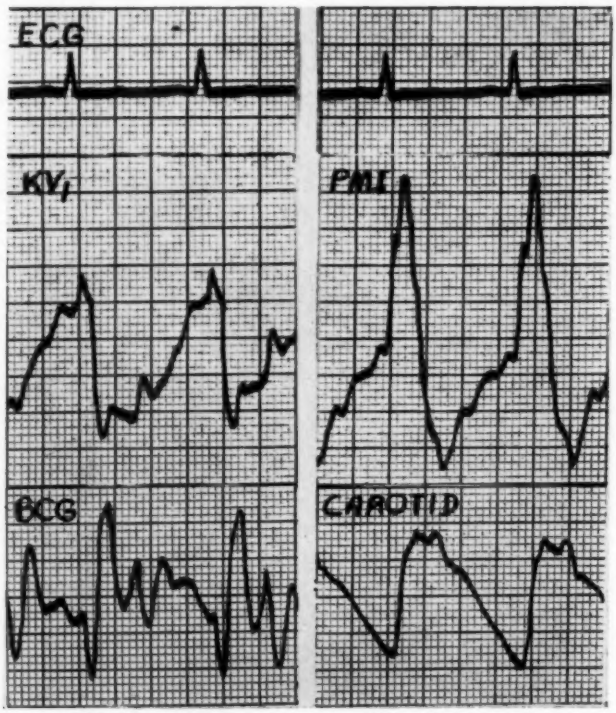

Fig. 3.—Trace taken from Patient 12. This patient exhibited moderate symptoms (Table I), moderate cardiac enlargement and electrocardiographic changes associated with left ventricular enlargement. Note that the outward movement in midsystole (KV_1 trace), which usually parallels the I-J upstroke in the ballistocardiogram, is diminished and actually in this instance occurs late. The apex thrust, as noted in the PMI trace, has now become markedly exaggerated and begins approximately 0.04 second after the onset of the QRS complex. This represents an early onset of the apex impulse, as compared to normal subjects. The retraction which usually occurs just preceding the apex impulse is only represented by a notch in the upstroke of the PMI. Note that the apex impulse is very sharp, terminating abruptly just after the onset of ejection, as determined by the upstroke in the carotid trace. This is followed by a rapid retraction of the apex, extending up to the time of the carotid incisural notch. Thus, as moderate symptoms and cardiac enlargement occurs, the apex impulse becomes markedly exaggerated and the retraction of the apical region of the chest, which just precedes the apex thrust in normal subjects, is absent.

just before the incisural notch of the carotid pulse, is replaced by a well-defined inward movement. Traces taken from the right lower parasternal region of the chest (KV_1) usually reveal a marked exaggeration of the inward movement of the chest during the early portion of ejection. The midsystolic outward movement, which parallels the I-J upstroke in the ballistocardiogram, is decreased in amplitude or absent (Fig. 3).

Group 4 (Marked symptoms, marked cardiac enlargement, electrocardiographic changes of left ventricular hypertrophy, and right- and left-sided congestive heart ailure): Fig. 4 is a representative trace taken from Patient 18. These three patients, as noted from Table I, are those with long-standing cardiac enlargement and symptoms. In addition, they differ from the other groups by having present both left- and right-sided congestive heart failure (right-sided failure is most prominent clinically, being manifested by peripheral edema, ascites, and enlargement of the liver). The trace taken from the point of maximal apex impulse has essentially the same features as those described for Group 3 patients, with a markedly increased thrust beginning early, about 0.04 second after the onset of the QRS complex (Fig. 4). The notch in the upstroke of the apex thrust

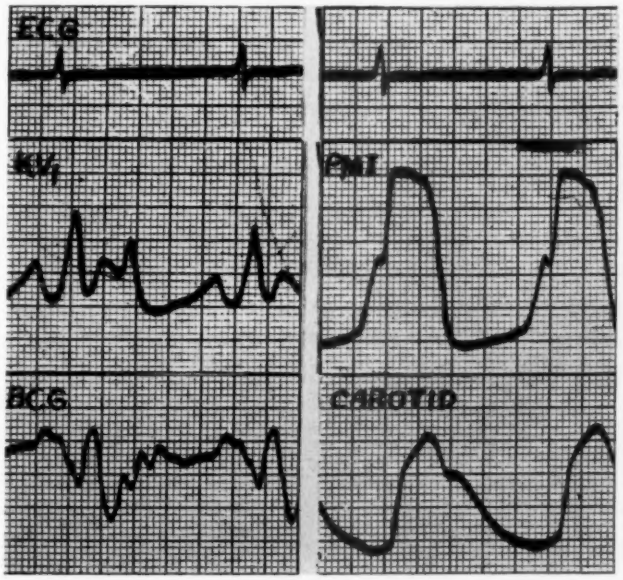

Fig. 4.—Trace taken from Patient 18 in which there were severe symptoms as the result of aortic insufficiency, with the presence of both left- and right-sided congestive heart failure. The KV_1 trace has a large outward movement (upward) which begins approximately 0.04 second after the onset of the QRS complex. The entire parasternal region of the chest is sustained above the diastolic or resting level of the chest during the ejection phase in contrast to a marked retraction in normal subjects, as well as in the other three groups of patients with aortic insufficiency. This trace is similar in some respects to that noted in patients with mitral stenosis and right ventricular hypertrophy. The trace taken from the point of maximal apex impulse again shows an exaggerated apex thrust. In this instance the apex thrust was of such great magnitude that the pickup device could not follow the entire outward movement which blunted the top of the impulse. The outward movement, which begins just before the onset of the QRS complex, is presumably due to auricular activity.

is completely absent. The traces from the KV_1 position are consistently different from those in Group 3. Instead of the marked retraction of the lower chest wall in early ejection, the precordium is usually sustained out above the diastolic or resting level of the chest during the entire ejection period. The initial outward movement begins 0.04 second after the onset of the QRS complex of the electrocardiogram and is relatively exaggerated when compared to traces from normal subjects or the comparable traces in the other groups of patients with aortic insufficiency. This is followed by some retraction during

ejection; however, the traces never dip below the diastolic or resting level of the chest. Similar traces in pattern have been noted from patients with right ventricular hypertrophy and from individuals with mitral stenosis.[4] Thus, in Group 4 subjects, in which there was present long-standing left- and right-sided congestive heart failure, the apex impulse is exaggerated and similar in configuration to that noted in Group 3 subjects; however, tracings taken over the lower parasternal region of the chest (KV_1) exhibit patterns which resemble those noted in tracings from patients with right ventricular hypertrophy or mitral stenosis.

DISCUSSION

As stated, the kinetocardiograms represent low-frequency precordial movements; however, as the configuration of the movements from many points over the precordium is generally not appreciated, a brief discussion as to some of the factors concerning the mechanisms of the movements seems pertinent. It is to be emphasized that the traces represent graphically the phenomena that can be palpated over the precordia. As the "untrained fingers" are rather crude instruments, the detail as represented in the traces cannot be fully appreciated at the bedside. However, it has been our experience that as one becomes more familiar with the patterns, many of these phenomena described in the present communication can be detected clinically. It has been recognized for many years that an exaggeration of the apex thrust is a very reliable sign of left ventricular hypertrophy; however, there are certain different features of the apex thrust in various diseases which can easily be detected clinically. For instance, the present study reveals the apex thrust to be markedly exaggerated in patients with aortic insufficiency, being a very abrupt movement and retracting markedly during the ejection period. In contrast to this, the apex thrust in aortic stenosis and hypertension is frequently sustained throughout the entire ejection period. Other movements over the precordium may also be appreciated clinically. The retraction of the parasternal region of the chest during systole is easily detected at the bedside, both in normal subjects and in patients with aortic insufficiency, by either palpation or careful observation of the region. Thus, the tracings, in essence, can serve as a valuable aid in understanding and recognizing the palpable phenomena over the precordium.

Although the movements of the precordium actually have been recognized clinically for many years, there is very little information as to the mechanisms for the various movements. It suffices to state that the chest-wall motion during the cardiac cycle is probably the result of the motions and impacts of the heart on the chest wall. In addition, during ejection and in early diastole, there are changes in the tracings which probably result from a volume or pressure change within the chest. An example of this is the normal retraction of the entire chest wall during the ejection period. Thus, as the movements and forces associated with the beating human heart have not been clearly defined, the genesis of the movements represented in the precordial traces is a matter of speculation.

Even though the mechanism for the various movements is uncertain, there are still several points which are of interest strictly from a pattern analysis.

The present study suggests a definite correlation between these low-frequency precordial movements (kinetocardiograms), and the functional status of the myocardium. Fig. 5 summarizes the changes noted in the tracings taken from the V-1 position in the functional categories previously described. The trace from the patient with only an auscultatory aortic insufficiency (Patient 1) is not too different from normal. In patients with minimal symptoms, the mid-systolic outward movement is exaggerated (Patient 3). As there are only two

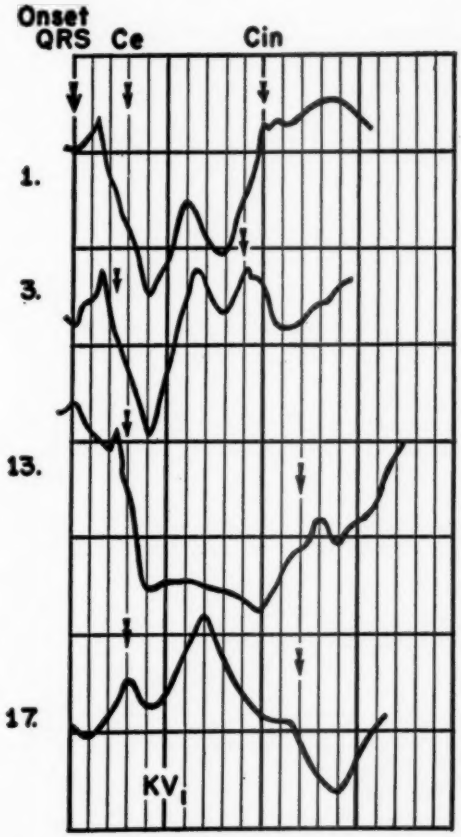

Fig. 5.—Drawing of the traces from the right parasternal region of the chest, the position corresponding to the V-1 lead of the precordial electrocardiogram. The vertical lines represent a time interval of 0.04 second. The onset of the QRS complex of the electrocardiogram is indicated by the first arrow, the second arrow (*Ce*) indicates the onset of ejection as determined by the upstroke of the carotid pulse, and the third arrow (*Cin*) represents the carotid incisural notch. The numbers at the left represent the patients from which the drawings were made. Note that the outward movement in midsystole (first outward movement after the onset of ejection—second arrow) is normal in amplitude in Patient 1, exaggerated in Patient 3, essentially absent in Patient 13, and markedly exaggerated in Patient 17. The parasternal region of the chest in Patients 1, 3, and 13 retracted during the ejection period (between *Ce* and *Cin*), while Patient 17 exhibited an outward movement during this time, similar in configuration to that noted in patients with right ventricular hypertrophy. In Patient 17, it can be noted from Table I, there was present right-sided, as well as left-sided, congestive failure. Thus, the precordial traces may be an aid in evaluating right ventricular hypertrophy in the presence of left.

patients in Group 2, it is uncertain whether the differences reported will be found consistently in all patients; however, the transition of the normal pattern noted in those patients with no symptoms or cardiac enlargement to those found in Group 3 and 4 is striking. Thus the finding of two patients with an intermediate

type trace probably justifies the separation into the groups listed. With moderate symptoms and moderate cardiac enlargement, there is a diminished midsystolic outward movement of the parasternal region of the chest (Patient 13). Note that the trace from Patient 17, with left- and right-sided congestive heart failure, shows the parasternal region of the chest to be sustained out above the diastolic or resting levels, similar to that previously reported to occur in patients with right ventricular hypertrophy.[4] Thus the pattern of the precordial traces may indicate the presence of right ventricular enlargement in the presence of

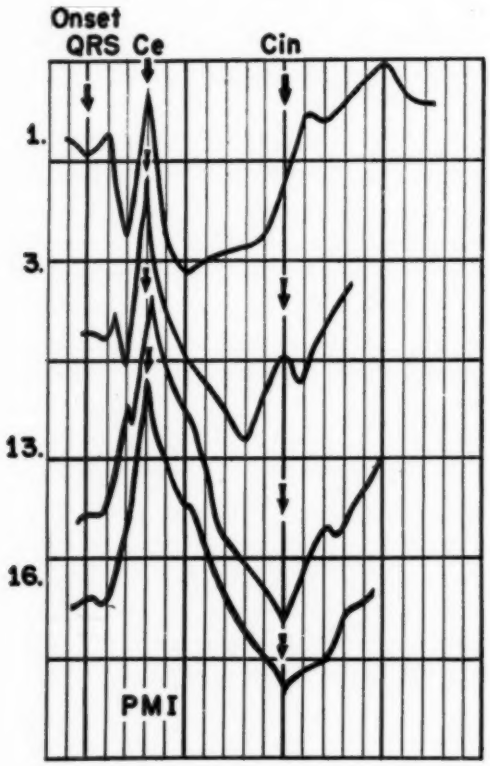

Fig. 6.—Drawing, taken from Patients 1, 3, 13, and 16, of the kinetocardiograms obtained at the point of maximal apex impulse. The first arrow represents the onset of the QRS complex of the electrocardiogram, the second arrow (*Ce*) represents the onset of ejection as determined by the upstroke in the carotid pulse, and the third arrow (*Cin*) represents the carotid incisural notch. This drawing is presented to represent the changes in the character of the apex impulse as the functional capacity of the patient progresses from no symptoms (Patient 1), to mild symptoms (Patient 3), to moderate symptoms (Patient 13), and to severe symptoms (Patient 16). The trace obtained from Patient 1 is within normal limits. With the development of mild symptoms, the apex impulse becomes exaggerated in amplitude (first outward movement before the onset of ejection or the second arrow). In addition, the retraction which just precedes the apex impulse diminishes in amplitude. As moderate symptoms develop (Patient 13) and cardiovascular enlargement occurs, the apex impulse is now markedly exaggerated in amplitude, beginning approximately 0.04 second after the onset of the QRS complex. The retraction, which usually just precedes the apex impulse, is probably represented now by a notch in the upstroke. Note that the apex impulse terminates very shortly after the onset of ejection with a marked retraction of the apical region of the chest. Note that the outward movement, which occurs just before the carotid incisural notch in tracings 1 and 3, is now reversed and is represented by an inward motion. Tracing 16 is not too markedly different from that noted in Patient 13. Thus there appears to be a correlation of the traces taken from the region of the apex impulse with the functional status of the patient.

left ventricular enlargement (Group 4 patients). Whether or not this generally will be characteristic is uncertain as there are only three patients in this group. It is possible that other factors, such as intraventricular septal bulging into the right ventricular cavity, may result in a similar pattern and not be related to right ventricular enlargement.

Fig. 6 is a drawing to illustrate the changes noted in the traces taken in the region of the point of maximal apical impulse. Note that in Patient 1, the trace is essentially normal in pattern. With minimal symptoms, as illustrated in Patient 3, there is a relative decrease in the retraction of the apical region of the chest just preceding the apex thrust and an exaggeration of the apex thrust. Patients in Groups 3 and 4 (Fig. 6) have similar patterns, characterized by a very marked increased apex thrust beginning earlier than normal (approximately 0.04 second after the onset of the QRS complex) and terminating approximately at the time of ejection. Note that there is an inward movement just preceding the incisural notch which is in contrast to an outward movement at this time as observed in normal subjects. Thus, the correlation of the kinetocardiographic patterns with the functional status of the heart and circulation suggests that the kinetocardiograms may offer a means by which the deterioration of the circulation and cardiac function in patients with aortic insufficiency may be evaluated objectively. This is actually as one would expect since the hemodynamics are abnormal in aortic insufficiency. Consequently, the movements and forces associated with each ventricular contraction and relaxation should be altered as the function of the heart deteriorates from the abnormal load imposed on the ventricle. The first response of the heart in aortic insufficiency to the stress of the regurgitation is probably an increase of the left ventricular forces. This apparently exaggerates the apex thrust even before electrocardiographic or x-ray changes result. While the exaggeration of the apex thrust is explained on the basis of increased left ventricular function or force, the early onset in patients with moderate cardiovascular difficulty is somewhat obscure. The only readily apparent explanation is that as dilatation of the ventricle occurs (which is a prominent feature in patients with aortic insufficiency), the electromechanical lag or the time from the onset of ventricular excitation to the onset of ventricular activity is decreased. If this should prove to be the explanation, the apex kinetocardiographic trace may be a valuable aid in detecting the presence of left ventricular dilatation in this group of patients.

It is well to point out that the hemodynamics in aortic regurgitation and mitral insufficiency are not similar as one might expect. The strain on the left ventricle in mitral insufficiency is primarily one of an increased inflow load as a result of the return of blood regurgitated into the auricle during the previous systole, plus the normal return from the pulmonary vascular beds. Although this would elevate the end-diastolic ventricular pressure, it is not comparable to that which is noted in aortic insufficiency. As a result of the incompetent aortic valve, the pressure load in the arterial bed is transmitted directly into the ventricle in aortic insufficiency, producing a foreloaded ventricular muscle.[5] Because of this or other unknown reasons, the precordial traces taken from patients with mitral insufficiency are not at all similar to those noted in aortic

insufficiency.[6] Fig. 7 is a drawing contrasting the patterns of the kinetocardiograms (traces from the right lower parasternal area and the point of maximal apical impulse) as noted in aortic insufficiency, mitral insufficiency, and normal subjects. The apex thrust in mitral insufficiency is not of the magnitude of that in aortic insufficiency. In addition, patients with mitral insufficiency

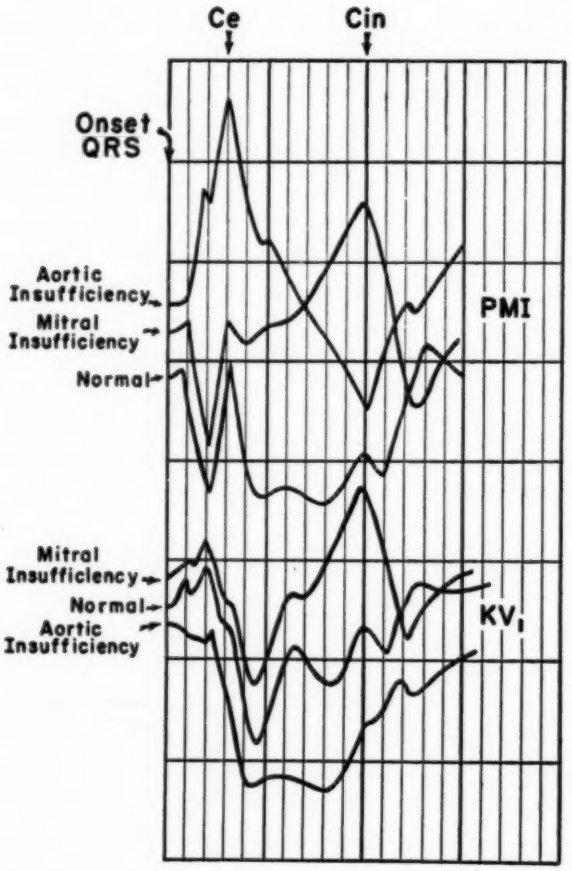

Fig. 7.—Drawing which represents the usual patterns of the precordial movements from normal subjects, patients with aortic insufficiency, and patients with mitral insufficiency. Traces from the point of maximal apex impulse are presented, as well as the right lower parasternal region of the chest (KV_1). The vertical lines represent a time interval of 0.04 second. The first arrow indicates the onset of the QRS complex in the electrocardiogram, the second arrow (*Ce*) the onset of ejection as determined by the upstroke of the carotid pulse, and the third arrow (*Cin*) represents the carotid incisural notch. The large outward movement of the apex thrust which terminates at the time of ejection (second arrow) is markedly exaggerated in patients with mitral insufficiency. Note that the trace taken from patients with aortic insufficiency exhibit a marked inward movement of the apical region of the chest during ejection, while patients with mitral insufficiency reveal an outward movement which reaches its peak about the time of the carotid incisural notch. Again note that the inward movement which just precedes the apex thrust in normal subjects, beginning 0.04 second after the onset of the QRS complex, is minimally represented in patients with aortic insufficiency, while it is well-marked in patients with mitral insufficiency. The KV_1 traces are not as dramatically altered as those from the point of maximal apex impulse; however, the traces taken from mitral insufficiency exhibit a well-marked outward movement of the precordium beginning in early systole, extending up to the time of the carotid incisural notch. Patients with aortic insufficiency of a moderate degree reveal a diminished or absent midsystolic outward movement which usually parallels the I-J upstroke in the ballistocardiogram.

exhibit a marked late systolic outward movement of the precordium (maximal at the apical region), while, in aortic insufficiency, the apical region of the chest moves inward in late systole. Thus, there appears to be a definite difference in the kinetocardiograms from patients with mitral insufficiency and aortic insufficiency, and a difference in the fundamental mechanisms of ventricular contraction and relaxation.

SUMMARY AND CONCLUSIONS

1. Kinetocardiograms (low-frequency precordial movements) were studied in eighteen patients with aortic insufficiency.

2. A definite correlation of the precordial movements with the functional status of the ventricular myocardium could be made as follows: (a) Normal kinetocardiograms occurred in patients with no symptoms or cardiac enlargement. (b) Patients with only minimal symptoms, or minimal cardiac enlargement, had an exaggeration of the apex impulse and a diminution in the retraction of the apical region of the chest just preceding the onset of the apex thrust. (c) Those with moderate cardiac enlargement and functional impairment had a markedly exaggerated apex impulse with only a notch present at the time of the normal early systolic retraction of the apex. In addition, there was absence, or a marked decrease, in the midsystolic outward movement of the parasternal region of the chest. (d) The patients in whom there was present right- and left-sided congestive heart failure revealed precordial pulsations from the parasternal region of the chest, similar in pattern to that noted in right ventricular hypertrophy. Traces taken from the region of the apex revealed markedly exaggerated apex thrusts as in the third group of patients.

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RELATIVE PULMONIC STENOSIS

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VALVULAR stenosis can be defined as an obstruction to the forward flow of blood at a valve orifice. The impedance to flow can result from a constricted valvular ring, the "organic form" of stenosis, or from dilatation of the chamber just proximal to it, the "relative form."

Although relative stenosis of the aortic and mitral valves has been repeatedly described in the past, scant attention has been directed to the existence of relative pulmonic stenosis.

Recently, we had the opportunity to study a patient in whom a pressure gradient of considerable magnitude across the pulmonary valve was not accompanied by any valvular abnormality on post-mortem examination. This led us to review all cases in our files in which a pressure gradient between the right ventricle and the pulmonary artery was present in the absence of any organic lesion of the pulmonary valve.

CASE REPORT

T. J. W., 4-year-old white boy, was admitted to the Children's Memorial Hospital in November, 1954, because of dyspnea, cyanosis, and marked limitation of exercise tolerance. These symptoms had been present from early infancy, at which time a cardiac murmur was also noted. The child's marked handicap was especially obvious after he learned to walk, and had become progressively worse until, at the time of admission, he was usually bedridden, either at a hospital or at home. He had had a series of respiratory infections which, more recently, had been associated with symptoms of congestive failure.

On physical examination he appeared thin and pale, and distinct cyanosis was present at rest. The cardiac apex was palpable in the fifth left intercostal space at the anterior axillary line. There was a Grade 3 systolic murmur heard loudest in the third left intercostal space parasternally. In the same area there was a short diastolic murmur beginning with the second sound. There was a distinct mid-diastolic murmur at the apex. A systolic thrill was palpable in the third left intercostal space. The pulmonary second sound was rather widely split, and normal in intensity. The femoral arteries were palpable. The liver edge was palpable 4 cm. below the right costal margin. There was no peripheral edema and the chest was clear.

X-ray (Fig. 1) showed a markedly enlarged heart with widening of the upper mediastinal shadow, both to the right and left, giving the cardiac silhouette the so-called "figure-of-eight" configuration. The vascularity of the lung fields was increased.

Cardiac catheterization was performed on March 10, 1955, and the pertinent data are summarized in Table I. The increased oxygen content in the superior vena cava indicated an anomalous venous return at this level, while the similarity of the systemic and the pulmonary arterial oxygen saturation was suggestive of a complete mixing of blood in the atria.

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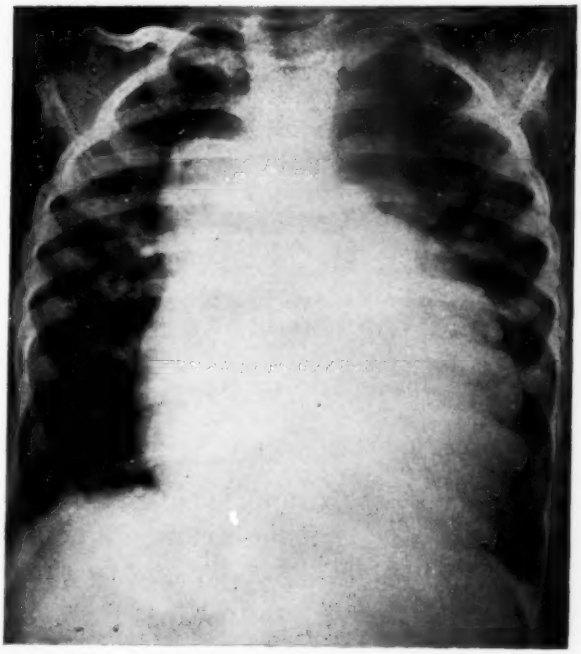

Fig. 1.—T. J. W., 4-year-old boy. Diagnosis: total anomalous pulmonary venous drainage with normal pulmonary valve. Posteroanterior roentgenogram of the chest, showing a typical "figure-of-eight" configuration of the cardiac silhouette, marked cardiac enlargement, and increased vascularity of the lung field.

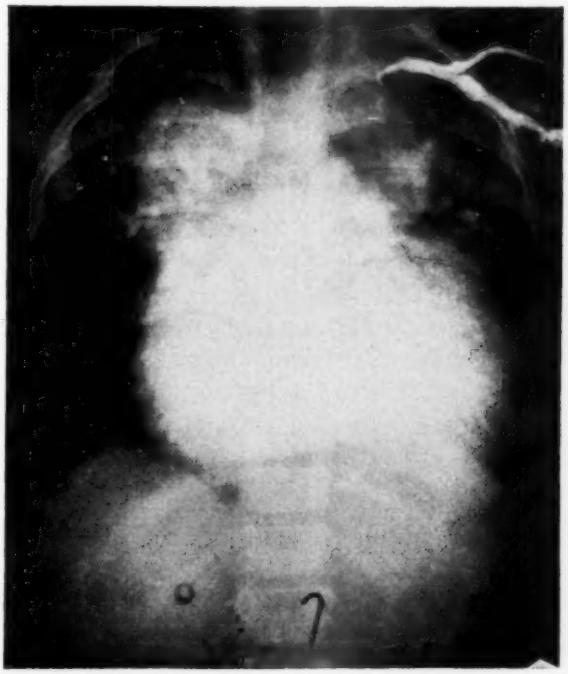

Fig. 2.—Same patient as in Fig. 1. Angiocardiogram showing a large vascular channel extending from the left hilum to the left innominate vein during the phase of pulmonary venous return.

Angiocardiography was performed on Aug. 10, 1955, to visualize the pulmonary venous system. In the phase of pulmonary venous return a large vascular trunk was visualized extending from the left hilum upward to communicate with the left innominate vein and thence the superior vena cava (Fig. 2).

Surgery was advised because of the poor outlook and failure to respond to medical treatment. At operation all pulmonary veins were seen to merge into a common venous trunk emptying into the left innominate vein. An anastomosis was performed between the mobilized upper end of the above common trunk and the left auricular appendage.

During the first postoperative hours the patient developed progressive pulmonary edema, which rapidly resulted in death.

Post-mortem examination revealed the following pertinent findings: (1) total anomalous pulmonary venous drainage into the left innominate vein; (2) widely patent foramen ovale; (3) right auricular and ventricular dilatation and hypertrophy; (4) hypoplasia of the left auricle; (5) pulmonary edema; (6) passive congestion of the organs.

DISCUSSION

Although the existence of relative pulmonic stenosis has been invoked to explain certain acoustic findings such as the systolic murmur in interatrial septal defect, proof of this has been possible only recently by cardiac catheterization studies.

Snellen and associates[1] reported two cases of total anomalous pulmonary venous drainage with a pressure gradient across the pulmonary valve of 10 to 15 mm. Hg. These authors suggest that the gradient probably was the result

TABLE I

LOCATION	O_2 CONTENT (VOL. %)	PRESSURE (MM. HG)
L.S.V.	10.8	
S.V.C.	15.7	
I.V.C.	12.55	
R.A.	15.7 15.0 14.45	8/3
R.V.	14.85 16.4 14.7	78/8
M.P.A.	16.1	36/10
R.P.A.	16.0	35/10
L.A.	15.6	7/2
F.A.	15.2 cap. = 18.5 sat. = 83%	95/60

L.S.V. = Left Subclavian Vein.
S.V.C. = Superior Vena Cava.
I.V.C. = Inferior Vena Cava.
R.A. = Right Auricle.
R.V. = Right Ventricle.
M.P.A. = Main Pulmonary Artery.
R.P.A. = Right Pulmonary Artery.
L.A. = Left Auricle.
F.A. = Femoral Artery.

of disproportion between a normal pulmonary valve area and an increased blood flow through it.

Blount and co-workers[2] later reported a case of interatrial septal defect in which a pressure gradient of about 20 mm. Hg between the right ventricle and the pulmonary artery disappeared after surgery. They also concluded that increased pulmonary flow was the direct cause of the relative pulmonary stenosis. The disappearance after closure of the defect was therefore explained by the return to normal of the pulmonary flow. A third case with post-mortem findings was reported by Rudolph and associates.[3] In this case a pressure gradient of

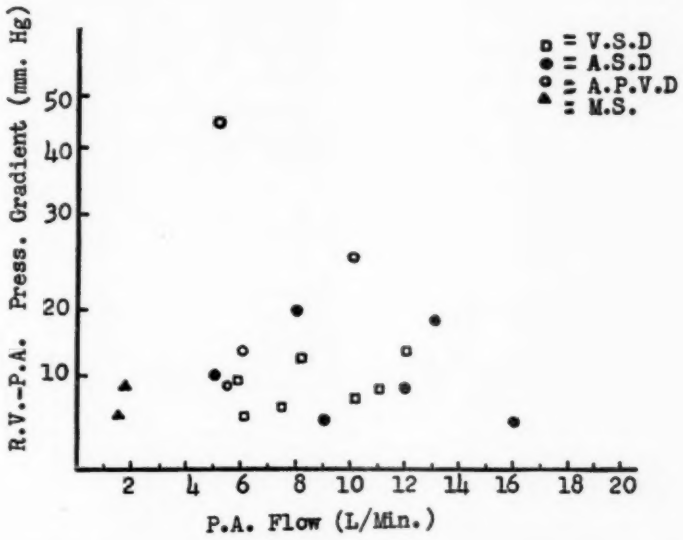

Fig. 3.—Scattergram illustrating the relationship between pressure gradient across the pulmonary valve and pulmonary artery flow in 19 cases of relative pulmonic stenosis. Please note the absence of any correlation between flow and pressure. *V.S.D.*, Ventricular septal defect; *A.S.D.*, atrial septal defect; *A.P.V.D.*, anomalous pulmonary venous drainage; *M.S.*, mitral stenosis.

33 mm. Hg across the pulmonary valve was recorded in association with a large left-to-right shunt through an interatrial defect. These authors suggested that the gradient probably originated in a disproportion between an abnormally large right ventricle and a relatively normal pulmonary valvular ring, rather than on the basis of an increased pulmonary flow directly.

Kjellberg and associates,[4] in a presentation of the clinical data from their cases of atrial septal defect, include a group with a distinct gradient in which organic pulmonic stenosis was ruled out. They also attribute this relative stenosis to the inability of a rather rigid pulmonic valvular ring to change size while the pulmonary artery above it and the right ventricle below may be markedly dilated.

Recently, Ellison and co-workers[5] carried out total pulmonary valvulectomy in dogs in an attempt to assess the hemodynamic alterations in pulmonic insufficiency. In all operated animals the right ventricular systolic pressure was greater than pulmonary systolic pressure, the average gradient being 15 mm. Hg and ranging from 2 to 40 mm. Hg. The two dogs in which the highest gradi-

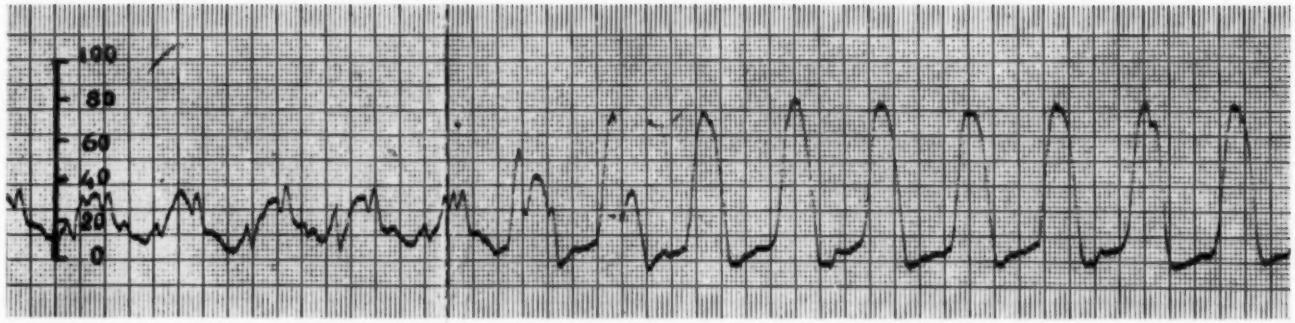

Fig. 4.—Same patient as in Figs. 1 and 2. Tracing obtained during withdrawal of the catheter from the pulmonary artery into the right ventricle, showing a pressure gradient of 42 mm. Hg in systole.

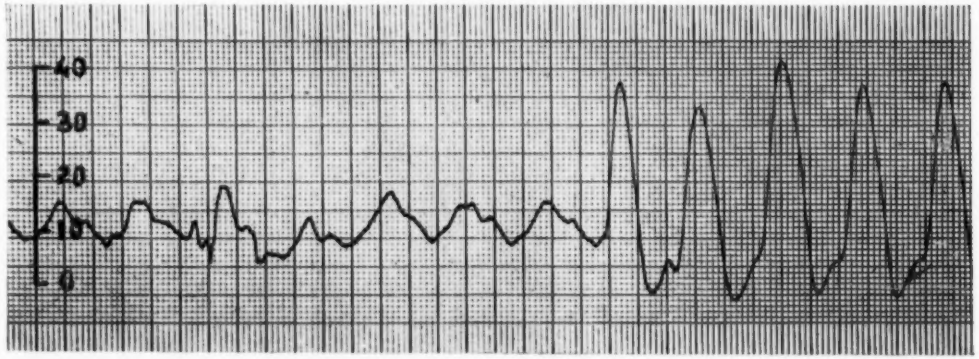

Fig. 5.—C. J. M., 9-year-old girl. Diagnosis: pulmonic valvular stenosis with normal aortic root. Tracing obtained during withdrawal of the catheter from the pulmonary artery into the right ventricle. Please note that, in contrast to Figs. 4 and 6, the right ventricular pulse is represented by a smooth hump with summit in mid-systole.

ents were recorded were autopsied and no obstruction at the valve orifice was found.

All cases catheterized in this hospital, in which a pressure gradient was recorded that was not attributable to organic pulmonary stenosis, were reviewed.

In the diagram (Fig. 3) the gradient between right ventricular and pulmonary artery pressures is plotted against the estimated pulmonary flow. It is clear that in these cases there is no direct relationship between flow and pressure gradient. In fact, we have studied patients with a very high pulmonary artery flow ranging between 4 to 10 times the systemic flow in whom there was no gradient across the pulmonary valve. Two of the cases in which a gradient was present (Fig. 3) had mitral stenosis with reduced cardiac output. Therefore, one may infer that the increase in pulmonary flow alone is not enough to explain the presence of a pressure gradient. It seems more likely that dilatation of the right ventricle, not accompanied by a comparable distention of the pulmonary valvular ring (which is in fact composed of less distensible tissue), is the principal factor producing relative pulmonic stenosis. However, it is realized that increased pulmonary flow may play an additional role in the genesis of the gradient and in its magnitude.

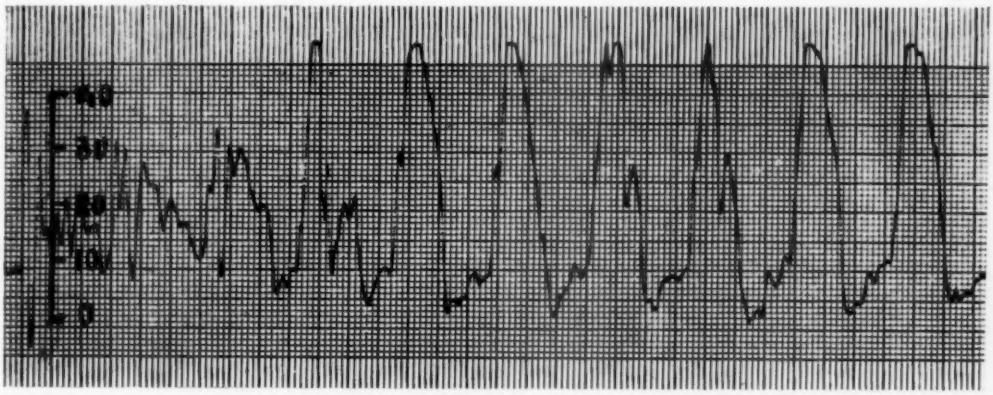

Fig. 6.—J. C. L., 3-year-old boy. Diagnosis: atrial septal defect with normal pulmonary valve. Pressure obtained during withdrawal of the catheter from the pulmonary artery into the right ventricle, showing a pressure gradient of considerable magnitude across the pulmonary valve.

The pressure curves recorded during withdrawal of the catheter from the pulmonary artery into the right ventricle (Fig. 4) were carefully reviewed to determine whether they had any characteristics to help distinguish organic from relative stenosis. It has been observed,[6] and repeatedly confirmed in this laboratory, that in pulmonic valvular stenosis, even in the mildest forms (Fig. 5), the right ventricular pulse is represented by a dome-shaped curve with a peak in mid-systole, resembling an isometric type of contraction. This is explained by the fact that, in pulmonic valvular stenosis, resistance to outflow is constant during ventricular systole since it is almost entirely produced by the stenotic valve.

In contrast, when the pulmonic valve is normal, its opening and closing generate sudden variations in resistance to outflow which are mirrored in the

pressure curve by characteristic angulations. In the case presented above, as well as in the other cases of which Fig. 6 is representative, the right ventricular pulse presents distinct systolic divisions suggesting a normal mechanism of opening and closure of the pulmonic valve.

The normal contour and the relatively high pressure of the pulmonary artery curve represent added evidence against organic stenosis.

It is interesting to note that in the case presented above, as well as in all other cases of anomalous venous return or interatrial defect with a considerable right ventricular-pulmonary artery pressure gradient observed by the authors, a thrill was noticed. This is in contrast to the usual uncomplicated case of interatrial defect in which a thrill is practically never felt.

SUMMARY

1. A group of cases presenting a pressure gradient across the pulmonary valve not associated with any valvular abnormality has been analyzed, and a representative case with pressure gradient of over 40 mm. Hg has been presented in detail.

2. The mechanism of relative pulmonic stenosis has been discussed. It has been concluded that increased pulmonary flow alone is not adequate to explain the pressure gradient.

3. Inspection of the pressure pulses usually gives important clues with which to distinguish relative from organic stenosis.

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ELECTROCARDIOGRAPHIC CHANGES OF LEFT VENTRICULAR HYPERTROPHY: EFFECTS OF ANTIHYPERTENSIVE TREATMENT

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INTRODUCTION

CONGESTIVE heart failure, commonly associated with left ventricular hypertrophy, has been recognized as the most common cause of death in hypertension.[1,2] In recent years, with the introduction of improved methods of treatment of congestive heart failure and the increasing availability of effective antipressor drugs, death due to intractable congestive failure as such (in the absence of evident coronary artery disease) has become an uncommon event.[3] However, the presence of left ventricular hypertrophy still maintains a considerable clinical significance. It may influence selection of and response to antipressor drugs, e.g., the choice of a ganglion-blocking drug instead of an agent which, like hydralazine, may increase cardiac work; it also determines the prescription of low-sodium diets, digitalis, and diuretics.

Hypertrophy of the left ventricle (with which we are most particularly concerned here) can be proved only by post-mortem examination. However, the diagnosis can be made with some confidence by physical examination or by roentgenography. The electrocardiogram contributes greatly to the diagnosis since certain characteristics appearing in standard limb,[4] unipolar limb, and precordial[5] leads show a distinct association with anatomically proved left ventricular hypertrophy. Scott and co-workers[6] evaluated the electrocardiographic criteria of Sokolow and Lyon[5] and confirmed the diagnosis anatomically in 85 of 100 cases, when the diagnosis was based on the presence of any single criterion of hypertrophy.

We selected certain of these electrocardiographic criteria of left ventricular hypertrophy as the area of this study. The aim was to determine the association of these electrocardiographic patterns of hypertrophy with the syndrome of malignant hypertension on the one hand, and with severe essential hypertension on the other, the association of these abnormal patterns with subsequent therapeutic responses, and the changes which occurred during treatment.

It will be shown (1) that the imposition of the syndrome of malignant hypertension only slightly alters the incidence and distribution of electrocardiographic criteria of hypertrophy from that of severe essential hypertension; (2) that pretreatment tracings are poor indications of the probability of success in antipressor therapy; (3) that, although diminution of electrocardiographic abnor-

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malities are more common in patients with good therapeutic responses than in those with poor responses, there is not a consistent association; (4) that, because of this variability in electrocardiographic response, serial tracings are of little assistance in assessing therapeutic response; and (5) that the scattered incidence of the individual abnormalities taken as criteria of hypertrophy makes it impossible to select any one of these as of exclusive or predominant diagnostic value.

MATERIAL AND METHODS

Records of 78 patients with severe essential hypertension or the malignant phase of essential hypertension were studied; no patient had evident congestive cardiac failure. The group was composed of fifty men and twenty-seven women, ranging in age from 25 to 70 years, and including one boy of 12 years. The average age of the adults was 45 years.

Patients with electrocardiographic evidence of left bundle branch block or myocardial infarction, or with clinical evidence of chronic valvular heart disease or angina pectoris were not included in this study. Since S-T-T changes due to digitalis and left ventricular hypertrophy cannot easily be differentiated, patients receiving digitalis were also excluded. Multiple lead electrocardiograms were available for every patient; each electrocardiogram had three standard limb, three augmented unipolar limb, and three to eight precordial leads. The diagnosis of left ventricular hypertrophy in each patient prior to treatment was based on the presence of one or more of eight electrocardiographic criteria adapted after Sokolow and Lyon,[5] as listed in Table I. Tracings made before and during an adequate trial of one or more antihypertensive agents given alone or in combination were analyzed. The periods of treatment ranged from 1 to 50 months, averaging 21 months. Twelve of the 78 patients died after less than 3 months of observation; 9 of these 12 patients had shown no response to therapy. Forty patients were observed for two or more years.

For convenience in the evaluation of response to treatment, patients were separated into two classes of hypertensive disease: (1) *severe essential* (35 pa-

TABLE I. CRITERIA FOR DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY MODIFIED AFTER SOKOLOW AND LYON[5]

A. Unipolar Limb Leads
   1. Upright T-wave in aV_R and S-T segment elevated 0.5 mm. or more
   2. Voltage of R-wave in aV_L > 12.5 mm.
   3. S-T segment depressed > 0.5 mm. in aV_L in case of horizontal heart or in aV_F in case of vertical heart
   4. T-wave flat, diphasic, or inverted, with R-wave 6.0 mm. or more in aV_L or aV_F and with (3)

B. Precordial Leads
   5. Voltage of R-wave in V_6 or V_5 plus S-wave in V_1 > 35 mm.
   6. S-T segment depressed 0.5 mm. in V_6 or V_5
   7. T-wave flat, diphasic, or inverted in leads V_6 or V_5, with normal R and small S-waves and with (6)
   8. Onset of intrinsicoid deflection in V_6 or V_5 > 0.05 sec.

tients) defined as a state of persistent diastolic hypertension, with retinal, cerebrovascular, cardiac, and/or renal evidence of advancing hypertensive vascular disease; (2) *malignant* (43 patients) defined as a syndrome characterized by papilledema, retinal hemorrhages and exudates, objective evidence of hypertensive heart disease, and proteinuria and hematuria, usually associated with impaired renal function and commonly accompanied by loss of weight.

A composite severity index was assembled for every patient, both before and during therapy, concurrently with each electrocardiogram. This index expresses numerically the over-all severity of the patient's disease at the time of observation, by assigning a maximum of four points each to estimates of (1) average daily hospital and home supine diastolic pressure, and of the extent of hypertensive vascular disease, (2) in the heart, (3) in the kidney, and (4) in the brain.[7]

Antihypertensive treatment consisted of hydralazine (1-hydrazinophthalazine) or ganglion-blocking agents (hexamethonium or pentapyrrolidinium), alone or combined, or in combination with reserpine. The majority of patients were treated with hydralazine alone. Two patients with essential hypertension had had bilateral thoracolumbar sympathectomy.

Response to treatment was classified according to change in average diastolic blood pressure. If the average diastolic pressure fell below 110 mm. Hg the patient was considered a responder, and if it did not, as a nonresponder. Twenty-nine of the 43 patients with malignant hypertension were classified as responders to treatment and 14 as nonresponders; 20 of the 35 patients with severe essential hypertension were responders and 15 were nonresponders.

RESULTS

1. *Pretreatment Electrocardiograms.*—

a. *Incidence of criteria of left ventricular hypertrophy (Table II):* In the whole hypertensive group, the mean number of electrocardiographic criteria of

TABLE II. INCIDENCE OF ELECTROCARDIOGRAPHIC CRITERIA FOR LEFT VENTRICULAR HYPERTROPHY AND TOTAL SEVERITY INDEX (T.S.I.) IN 78 HYPERTENSIVE PATIENTS

	NUMBER OF PATIENTS	BEFORE TREATMENT		AFTER TREATMENT	
		AVERAGE NO. CRITERIA	AVERAGE T.S.I.	AVERAGE NO. CRITERIA	AVERAGE T.S.I.
Hypertensive Patients	78	5.0	8.1	4.8	6.0
Responders	49	4.4	7.6	3.7	4.2
Nonresponders	29	5.6	8.5	5.9	7.7
Malignant Hypertension	43	5.2	9.2	5.1	6.9
Responders	29	4.6	8.9	4.2	4.8
Nonresponders	14	5.8	9.5	5.9	9.0
Essential Hypertension	35	4.8	6.9	4.5	5.0
Responders	20	4.2	6.3	3.2	3.6
Nonresponders	15	5.4	7.4	5.8	6.4

left ventricular hypertrophy present in tracings prior to treatment was 5.0 (range 1 to 8). The mean incidence was somewhat greater (5.6) in patients who did not respond to treatment than in those who did (4.4), and in this respect corresponded to the respective estimates of severity of the hypertensive disease, which was greater in the nonresponders. In comparing the diagnostic groups, the criteria of hypertrophy were on the average more frequent and severity indices higher in patients with the malignant syndrome than in those with severe essential hypertension, and in both of these groups, greater in those who did not respond to treatment than in those who did. These differences, however, were small and the ranges of variation wide.

In addition, there was no consistent relationship between the number of positive criteria and (a) known duration of hypertension, (b) degree of roentgenographic evidence of cardiac hypertrophy, and (c) height of the diastolic pressure. Some patients with large hearts, as evidenced by clinical or x-ray examination, often had no more, or even fewer, criteria indicative of left ventricular hypertrophy than did patients with little or no evidence of significant cardiac enlargment (Figs. 1 and 2).

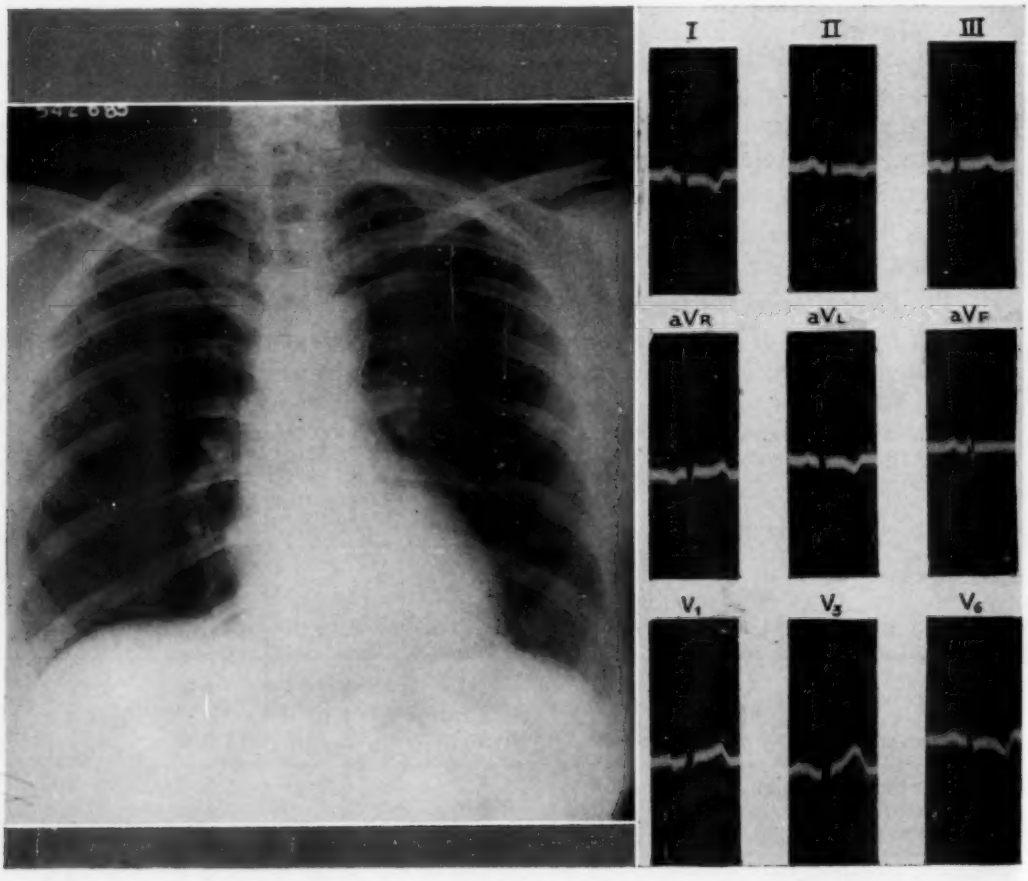

Fig. 1.—C. F., 38-year-old woman, with severe essential hypertension of 7 years' duration. Electrocardiogram shows 7 criteria of left ventricular hypertrophy including increased QRS voltage in Leads aV_L, V_1 and V_6, and abnormal S-T-T patterns in Leads aV_L and V_6. The transverse cardiac diameter of the heart by x-ray is normal (according to Ungerleider-Clark scale).

b. *Distribution of electrocardiographic criteria of left ventricular hypertrophy (Table III):* The most common criteria indicative of left ventricular hypertrophy were increased voltage of QRS complexes in Leads aV_L and/or precordial leads. Depressed S-T segments and abnormal T-waves, the so-called "strain pattern," were a little less frequently observed. All abnormalities, including delayed intrinsicoid deflections, were somewhat more often observed in tracings of patients with malignant hypertension than in patients with severe essential hypertension. Abnormal S-T-T patterns or increased voltage of QRS complexes as the sole criterion were present in a minority of patients (26 per cent).

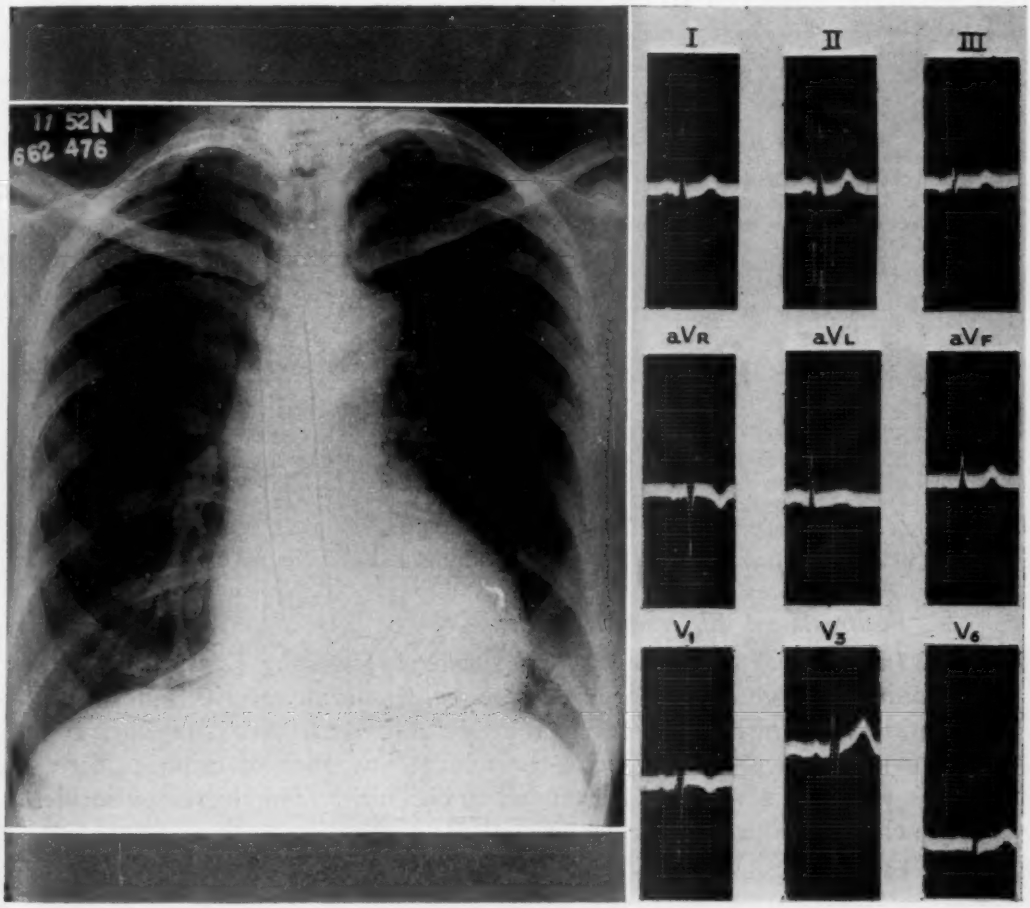

Fig. 2.—M. R., 48-year-old woman, with severe essential hypertension of 3 years' duration. The transverse cardiac diameter measures 15 cm., approximately 20 per cent above average in size. The electrocardiogram is normal.

This minority, with localized electrocardiographic changes, tended to exhibit a slightly higher incidence of favorable therapeutic responses than did patients with multiple electrocardiographic changes.

The distribution of the criteria of hypertrophy was grossly similar in the two diagnostic groups. Both abnormal QRS voltage and S-T-T changes were

only slightly more frequent in the malignant than in the severe essential group. However, delayed intrinsicoid deflection in Leads V_6 or V_5 was much more commonly observed in the malignant group.

TABLE III. DISTRIBUTION OF ELECTROCARDIOGRAPHIC CRITERIA OF LEFT VENTRICULAR HYPERTROPHY

	ALL PATIENTS: 78		RESPONDERS TO ℞: 49		NONRESPONDERS TO ℞: 29	
	NUMBER OF PATIENTS	PER CENT	NUMBER OF PATIENTS	PER CENT	NUMBER OF PATIENTS	PER CENT
Before Treatment						
Abnormal ST-T patterns	63	81	36	73	27	93
Abnormal ST-T patterns alone	6	8	4	8	2	7
Abnormal QRS voltage	72	92	45	92	27	93
Abnormal QRS voltage alone	14	18	12	24	2	7
Delayed intrinsicoid deflection	20	26	11	22	9	31
After Treatment						
Normal	8	10	8	16	0	0
Abnormal ST-T patterns	60	77	32	65	28	96
Abnormal ST-T patterns alone	7	9	4	8	3	10
Abnormal QRS voltage	62	79	36	73	26	90
Abnormal QRS voltage alone	8	10	7	14	1	3
Delayed intrinsicoid deflection	20	26	11	22	9	31

2. *Posttreatment Electrocardiograms.*—

a. *Incidence of criteria of left ventricular hypertrophy (Table II):* In the group manifesting good therapeutic responses, the mean severity index and the average incidence of criteria of left ventricular hypertrophy decreased; in patients nonresponsive to treatment the average number of criteria increased although the total severity index tended to diminish. The decreased incidence of these changes noted in tracings of patients responsive to treatment was also demonstrable in both diagnostic groups. However, in both malignant and essential hypertensive responders, the estimated extent of electrocardiographic improvement lagged behind the corresponding estimate of mean severity index, presumably because the level of diastolic pressure is so large a factor in the evaluation of severity.

It should also be noted that electrocardiograms of some patients, in both response and nonresponse groups, did not change during treatment, and that some classed as responders even showed additional evidences of left ventricular hypertrophy during treatment. Hence, the means estimated in the tables do not necessarily reflect uniform trends in incidence of electrocardiographic abnormalities.

b. *Distribution of electrocardiographic criteria of left ventricular hypertrophy after therapy:* In patients who responded to treatment, S-T-T and QRS abnormalities tended to diminish in frequency, but delayed intrinsicoid deflections persisted in each instance (see Table III). The electrocardiograms of 16 per cent (8 patients) of the response group became completely normal. In the nonresponse group, complete reversion of the tracing to normal during treatment was not seen. After treatment electrocardiographic abnormalities improved or disappeared in 31 per cent of all patients studied. Forty-one per cent of patients in the response group showed improvement as compared to 14 per cent of patients not responding to therapy (see Table IV).

TABLE IV. ALTERATIONS IN ELECTROCARDIOGRAMS AFTER ANTIHYPERTENSIVE TREATMENT COMPARED WITH TOTAL SEVERITY INDEX OF HYPERTENSIVE DISEASE (T.S.I.)

	NUMBER OF PATIENTS	PER CENT OF PATIENTS	AVERAGE T.S.I. BEFORE TREATMENT	AVERAGE T.S.I. AFTER TREATMENT	ECG NORMAL OR IMPROVED	
					NUMBER	PER CENT
Hypertensive patients	78	100	8.1	6.0	24	31
Responders to treatment	49	62	7.6	4.2	20	41
Nonresponders to treatment	29	38	8.5	7.7	4	14

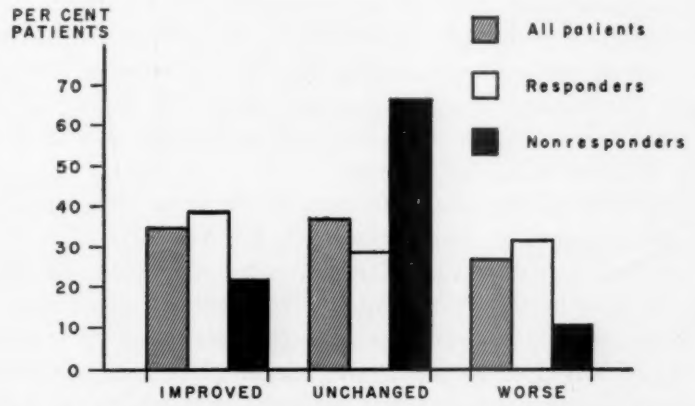

Fig. 3.—Changes in electrocardiographic criteria for left ventricular hypertrophy in 40 hypertensive patients after antihypertensive treatment from 2 to 4 years.

Doyle,[8] in a review of electrocardiograms of patients with hypertensive cardiovascular disease treated by methonium compounds, found a correlation between disappearance of electrocardiographic abnormalities and duration of treatment; about 90 per cent of patients treated for one year or more had improved electrocardiograms. In our series, 40 patients were observed for treatment for periods of 2 or more years. Electrocardiographic improvement occurred in only 12 (39 per cent) of 31 patients who had a satisfactory response to therapy, and in 14 (35 per cent) of the entire group (Fig. 3).

DISCUSSION

The severity of the hypertensive vascular disease in the group of patients studied is reflected in the high percentage of pretreatment tracings which showed S-T-T changes (81 per cent) and abnormal QRS voltages (92 per cent). The frequent concurrence in the tracings of more than one electrocardiographic criterion (average 5.0) can be presumed to enhance the accuracy of electrocardiographic diagnosis of left ventricular hypertrophy in this group, and in addition has permitted evaluation of some of these criteria separately as to their incidence and association with clinical status and therapeutic response.

The incidence and type of criteria of left ventricular hypertrophy found in pretreatment electrocardiograms were not guides to subsequent therapeutic response in individual patients, although the average incidence of these criteria was less in the group with adequate therapeutic responses. Eight per cent of the responders showed complete disappearance of abnormal S-T-T patterns, and 19 per cent had a return to normal of the abnormal QRS voltage. This tendency of increased voltage to revert to normal was particularly evident in patients who had essential hypertension and were responsive to treatment (25 per cent). In 8 of the 49 patients who had a satisfactory response to therapy, increased QRS voltage and abnormal S-T-T patterns disappeared completely during treatment.

The relative importance of one electrocardiographic criterion over another in the diagnosis of clinically significant cardiac hypertrophy could not be determined because of a lack of adequate necropsy material, plus the fact that different positive criteria were either present alone or, more frequently, in many and varying combinations. Although improvement was observed predominantly in electrocardiograms of patients responsive to antihypertensive therapy (41 per cent), favorable electrocardiographic changes of similar type and degree were observed as well in some patients nonresponsive to therapy and otherwise exhibiting progression of their vascular disease.

Probably because of the many factors other than true hypertrophy that contribute to electrocardiographic abnormalities, the study of serial electrocardiograms does not appear to be of much help as a means of estimating the success or failure of present-day therapy. From this it seems that the electrocardiogram considered alone does not accurately reflect the extent of hypertensive heart disease in an individual patient. In general, after treatment with available antipressor agents, electrocardiographic abnormalities which are attributable to left ventricular hypertrophy secondary to hypertension disappear or improve in about 30 per cent of all patients. Such improvement was 3 times more common in patients classed as responders—i.e., those with diastolic pressure averages of less than 110 mm. Hg—than in those listed as nonresponders, although the latter group showed significant improvement in over-all severity index.

SUMMARY AND CONCLUSIONS

Electrocardiograms of 78 patients with severe essential hypertension, including 43 in the malignant phase, were studied with reference to electrocardiographic evidence of left ventricular hypertrophy, before and during use of one or more antihypertensive drugs. The criteria for left ventricular hypertrophy were

adapted from those of Sokolow and Lyon[5]; the relative severity of the hypertensive disease (severity index) was estimated concurrently with each electrocardiogram.

The variable incidence of the separate criteria of hypertrophy (increased QRS voltage, S-T segment and T-wave changes) does not permit the selection of any one of them as having exclusive or predominant diagnostic value. The presence of the syndrome of malignant hypertension only slightly changes the incidence and distribution of electrocardiographic evidence of left ventricular hypertrophy.

Pretreatment electrocardiograms in this group of hypertensive patients had no predictive value as to the success or failure of subsequent therapy. Electrocardiographic improvement was more common in those patients who had a satisfactory response to therapy, but this was not a consistent association. Because of this variability, routine serial tracings add little to estimates of therapeutic response.

There was no consistent relationship between height of the blood pressure, total severity indices, size of the heart by teleroentgenogram, and the electrocardiographic changes attributable to left ventricular hypertrophy. Thus, while electrocardiographic estimates follow group trends rather closely, they do not accurately reflect the cardiac or even the over-all status of individual patients with hypertensive heart disease.

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FURTHER STUDIES OF THE ELECTROCARDIOGRAPHIC SPATIAL MAGNITUDE CURVE (IN THE RABBIT)

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IN A previous study of the shape of the QRS wave of the spatial magnitude curve of the cardiac electric vector[1] it has been reported that the gross irregularities in the spatial magnitude curve appeared to obey a general determining relation. It was found that a linear relation held between the time of first appearance of each irregularity and the time of occurrence of the maximum effect of the irregularity. It seemed that this observation merited further study in the animal heart for both gross and small irregularities. A refinement in technique by the use of automatic computing apparatus[2] has made it possible to study the finer details of the spatial magnitude curve. We have selected the rabbit for this study since it is well suited for procedures which interfere with the normal cardiac electrical activity.

The spatial magnitude curve is theoretically a measure of the magnitude of the cardiac electric vector in relation to time; the three-dimensional vector loop is a measure of the magnitude of the cardiac vector primarily as a function of direction. For reasons which have been discussed,[2] it seems possible that the present approach through study of the spatial magnitude curve may present a useful transformation of the available electrocardiographic evidence.

The irregularities have been studied both in the normal animal and under various interfering procedures which produced modifications in the polarizing properties of cardiac muscle. The modifications included those produced by phenol-induced injury to the myocardium, infarction induced by ligation of coronary arteries, potassium chloride interference with surface polarization, and ectopic beats induced either by aconite or pin-prick stimulation.

EXPERIMENTAL METHODS

Spatial magnitude curves of the (Duchosal-Sulzer) equivalent cardiac vector were obtained on a series of rabbits and on a few human patients. The methods and automatic equipment used have been previously described.[2] In many cases the square of the spatial magnitude curve has been recorded, as this often obviated the necessity for extreme high-frequency emphasis in observations on small fast irregularities. Gauge 20 needles (insulated except at the

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tip) were inserted intramuscularly in four positions according to the electrode system of Duchosal and Sulzer. This configuration of electrodes placed the heart at the center of a 9 cm. cube. All records were obtained with animals lying on their backs.

Records were made on 70 mm. photographic paper run at speeds in the range of 300 to 750 mm. per second, and each individual record lasted from 2 to 5 seconds (including from 8 to 20 heart beats). A series of preliminary experiments was performed using 15 animals. With subsequent refinement of technique and apparatus, a further series of 25 animals was studied. The animals used were adult rabbits of both sexes, and average weight of 2 Kg. Standard operative procedures, including tracheotomy, were used. Gallamine triethiodide combined with manual control of respiration permitted the maintenance of flaccidity and resulted in a considerable reduction in interference from muscle potentials and the effects of respiratory movement. The use of relatively short time-constant coupling circuits (high-pass filters) further reduced the effects of the latter factor.

Thoracic or abdominal exposure of the heart was employed and the pericardium was removed completely in all cases. Control records were obtained before, during, and after significant stages in the procedure.

Localized destruction of heart muscle was produced either by ligation or clamping of one of the larger branches of a coronary vessel, or by the injection of 1 to 3 minims of pure phenol into the myocardium. The depth of the injection in the latter case was such as to avoid either a subepicardial spread or an injection into the ventricular chamber. This method has been used satisfactorily on the dog heart to produce rapidly a localized area of necrosis.[3] The damaged area was accurately defined by dissection after death.

Local depolarization due to potassium was produced by placing on the myocardium pledgets of filter paper (area 1 sq. mm.) which had been soaked in a 1 M solution of potassium chloride. Partial reversal of this interference was achieved by removing the pledget and subsequently washing the heart with isotonic saline.

Ectopic beats were induced either by pin-prick stimulation of the myocardium or by the use of pledgets moistened with 2 per cent aconite. In some cases the aconite pledget was removed (though spontaneous production of ectopic beats continued) and a potassium chloride pledget placed on the same region.

In all our experiments we used five positions on the heart for the localized procedures, defined as follows: (1) left ventricle, apex; (2) left ventricle, anterior surface, midway apex-base; (3) left ventricle, left border, midway apex-beat; (4) right ventricle, apex; (5) right ventricle, anterior surface, two-third apex to base. These were chosen purely for convenience, and for reasons of practicability the posterior wall of the left ventricle was not included.

OBSERVATIONS

Spatial magnitude curves recorded from normal animals (40 cases) showed considerable variations. The majority of the curves included higher frequency

components or irregularities which were readily seen, when recorded by apparatus with a response from 1 c.p.s. to 5 k.c.p.s. Some typical curves for a human subject, and for several animals, are shown in Fig. 1. In traces *i*, *ii*, *iii* the lower curve of the pair, and the curve of trace *iv*, represent the spatial magnitude curve under the influence of various high-pass filter circuits. Variations of effective filter cutoff frequency were introduced by adjustment of the time constant of

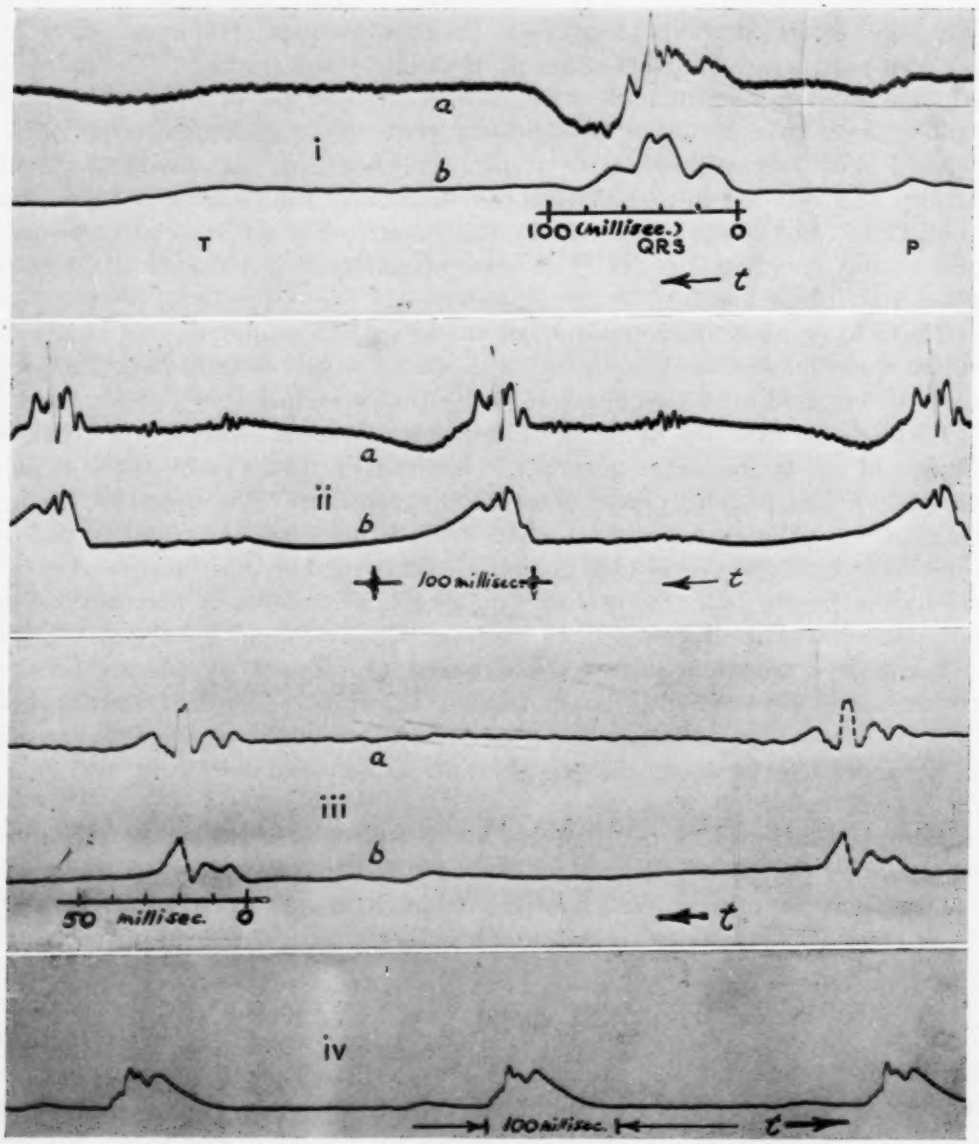

Fig. 1.—A set of typical spatial magnitude electrocardiograms (see text).

***i*, Human subject. *a*, The spatial magnitude curve after modification by a circuit which emphasized parts of the higher frequency spectrum. *b*, The ordinary spatial magnitude curve.**

***ii*, Normal rabbit spatial magnitude curve—the square of the curve was recorded in this trace: *a*, through a high-frequency emphasizing circuit; *b*, through a high-pass filter circuit with a cut off frequency of 5 c.p.s.**

***iii*, As *ii* above, but from a different animal; the high-pass filter had a cut off frequency of 0.5 c.p.s.**

***iv*, As *ii* and *iii*, from a further animal; the high-pass filter had a cut off frequency of 5 c.p.s.**

resistance-capacity coupling circuits. The upper curve of traces *i*, *ii*, *iii* represents the spatial magnitude curve under the influence of a high-frequency emphasis circuit.

Note that specification of the high-pass filter cutoff frequency as f_c means that components at this frequency were attenuated by 3 db. with respect to those at a mid-frequency, say 100 c.p.s. Components at frequencies below f_c would thus be further attenuated, at a rate increasing by 6 db. per octave. The long decay time in several of the curves is of no consequence for the present study since it only characterizes the effect of the high-pass filter. As far as this study is concerned, only the time location of higher frequency components after the start of the QRS complex is important. It must be pointed out that time relations of events in the QRS complex cannot be directly analyzed from the upper curves of Fig. 1, since the high-frequency emphasis circuit introduces quite complex phase-frequency relations. The circuit has been useful for determining the presence of high-frequency components. However, the phase variations introduced by the high-pass filters usually employed (R-C sections) were small for most important components. Generalizing, it may be said that many significant components appeared in the range from roughly 10 c.p.s. to 1 k.c.p.s.

We have observed that in most normal cases there were between three and six major high-frequency components in the spatial curve. These components appeared to occupy 80 to 90 per cent of the total QRS duration. In many cases for any one animal, it was possible to trace each of the components occurring in the normal curve throughout all subsequent curves, irrespective of the experimental procedures.

Each component remained invariant in time-location but alterations in amplitude frequently occurred in one or more components. It is only possible to say that different components alter in different ways under various procedures. As yet no reproducibility in the amplitude changes observed in different animals under identical procedures can be discerned.

Typical behavior during some experiments is illustrated in Figs. 6, 7, and 8. This shows the extensive alterations in the spatial magnitude curve which often appeared. Note that irregularities even so fast as 500 c.p.s. have appreciable magnitude.

A. *The Determining Relation for Irregularities.*—Close study has led us to describe the high-frequency irregularities in the curves as in our previous investigation of human patients[1] (Fig. 1). We have attempted to distinguish peaks and minima. A "peak" may be described as a reasonably narrow elevation over the neighboring shape or plateau of the curve and is measured at the highest point. In some cases a "peak" appeared as the start of a sudden decay of the curve.

A "minimum" is described as the lowest point of a trough—the lowest point below the neighboring sections of a curve taking account of any general environmental slope. Any confusion arising from the use of these definitions could often be resolved by study of the curve with a further accentuated high-frequency spectrum.

Throughout all the curves studied only one relation between "peaks" and the "minima" could be recognized. It was found that for many "peaks" subsequent "minima" could be located for which the following relation held (within experimental limits):

$$t_m = kt_p + c \quad \ldots\ldots\ldots \quad (1)$$

The factors "k" and "c" are constants; "t_p" is the time, in milliseconds, of occurrence of any given peak after the start of the QRS wave; "t_m" is the time of occurrence, in milliseconds, of the associated "minimum" after the start of the QRS wave; in the animal experiments "k" = 1.37 ± 0.11 and "c" = 0.36 milliseconds.

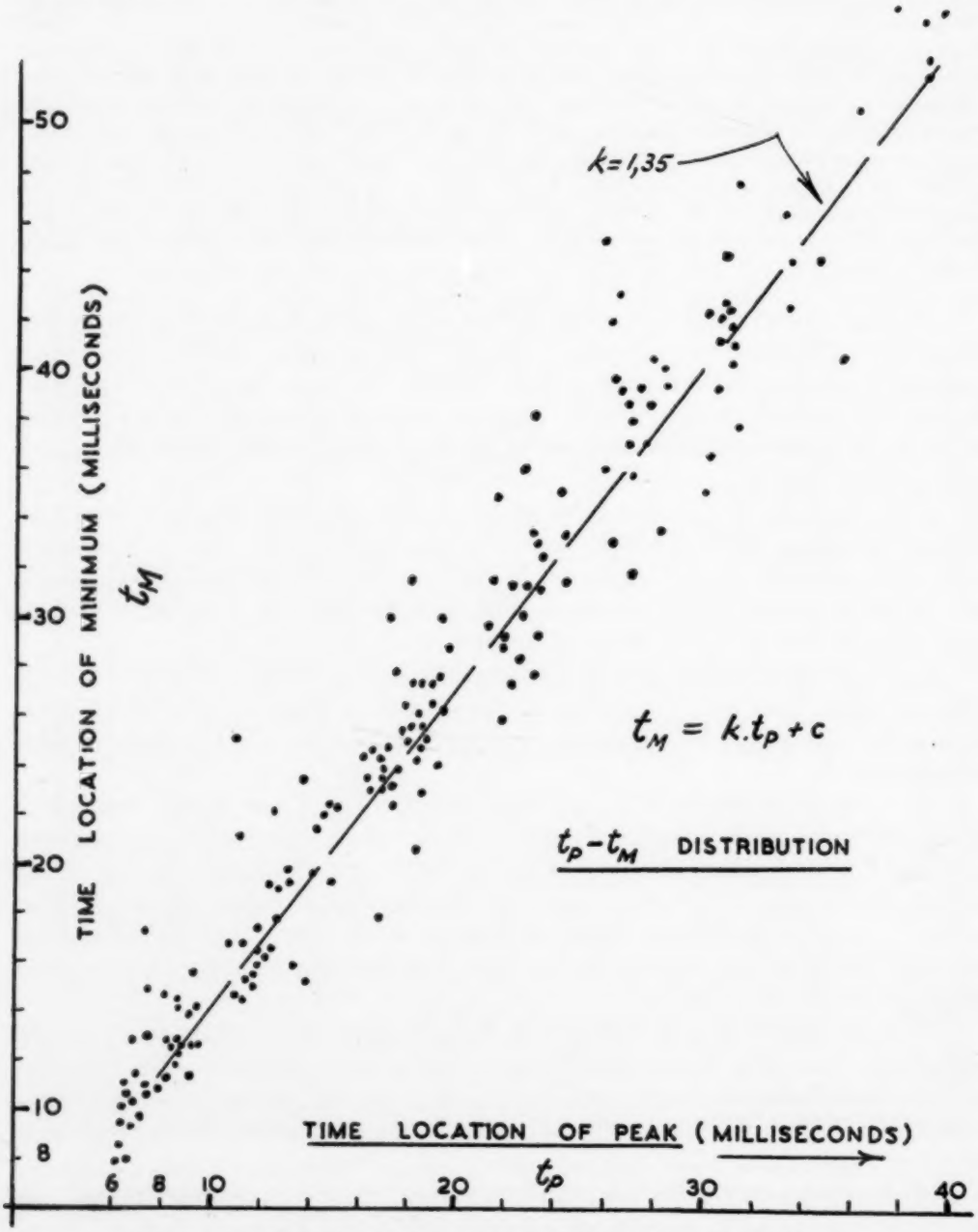

Fig. 2.—The distribution of time locations of peaks and associated minima, showing agreement with the relation quoted.

The relationship (1) was found to hold for all the rabbits studied throughout all experimental procedures except ectopic beat production. There does not appear to be any identifiable relation between the heights of peaks and the heights of minima, or any function of these. Peaks have been observed for which corresponding minima could not be seen. Occasional high-frequency fluctuations appeared which rose and fell rapidly. These components cannot be specified by the relation (1). These often occurred during our early experiments when the need for adequate high-frequency emphasizing apparatus was not fully appreciated. In our later experiments (with 25 animals) record segments numbering about 1,000 were taken (each of several seconds' duration), involving various procedures and times. A random sample of these indicated that about 15 per cent of peaks could not be matched with associated minima. Furthermore about 10 per cent of peaks and apparently associated minima could not be satisfactorily accounted for by the relation (1)—i.e., the specifying point on Fig. 2 fell outside the line defining twice the standard deviation from the mean.

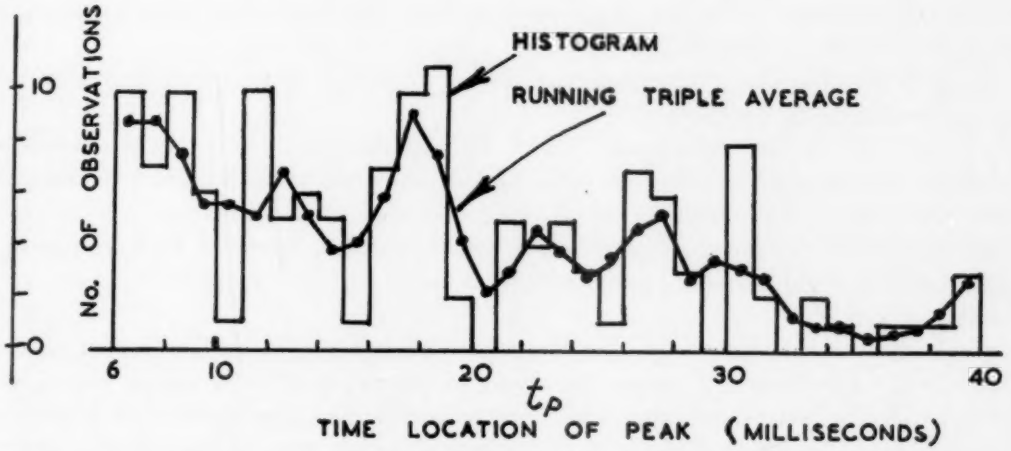

Fig. 3.—Histogram and smoothed frequency distribution of time location of peaks; the latter distribution was obtained by averaging at each time location point over three sequential values.

The relation (1) was found to apply in general independently of duration of the QRS complex; the $t_p - t_m$ distribution is illustrated in Fig. 2. The histogram or frequency distribution of time locations of peaks (t_p) is shown in Fig. 3 which also shows the running triple average. In both these curves there are clearly marked null regions of t_p in which few peaks occurred. The points of Fig. 2, and hence the observations for Fig. 3, were obtained from various conditions of experimental interference as well as from normal animals.

B. *The Form Factor in Myocardial Destruction.*—We have previously introduced the notion of "Form Factor."[1] This function is defined as the ratio of the area under the QRS curve of the spatial magnitude electrocardiogram to that of the rectangular frame which just completely encloses it. We have suggested that in the case of myocardial infarction in man, the Form Factor

after injury rises steadily over the period of healing and does not appear ultimately to return to near normal values.

In the present study we have observed the changes in Form Factor, as a function of time, after a small area (ca 1 sq. mm.) of cardiac muscle death was induced by phenol injection or by ligation of a branch of the coronary arteries. We have used 9 animals and followed the progress of the Form Factor for up to 100 minutes after the experimental interference. The Form Factor was computed from spatial magnitude curves using apparatus of high-pass filter cutoff frequency of 0.5 c.p.s. (using the normal not squared spatial magnitude curves).

In each case as can be seen from Fig. 4, the Form Factor showed a slight drop followed by a general rise to a magnitude appreciably greater than that in the normal animal. These results confirm in more detail the observation we have first reported on human patients having myocardial infarction.

However, when a small pledget of blotting paper soaked in potassium chloride was placed on the myocardium, a change in Form Factor occurred which was reversible. Within several minutes the Form Factor returned to its normal value in each case. The last four curves of Fig. 4 show the reversible variations of Form Factor in typical cases.

It is possible that these observations (if confirmed more generally) may be of some diagnostic interest.

C. *The Spatial Magnitude Curve During Ectopic Beats.*—Ectopic beats induced by pin-prick stimulation often produced curves with two main segments. The duration of the curve in some cases exceeded 90 milliseconds. Very few high-frequency components were observed. In cases wherein high-frequency components could be seen, peak-minimum pairs did not appear to satisfy relation (1).

An interesting property of the spatial magnitude curve is illustrated in Fig. 5. In the figure, *i* shows the effect of pin-prick stimulation in the close vicinity of the left ventricular apex. In *ii* and *iii* the experiment has been repeated, but a pledget soaked in potassium chloride was placed on the same region, prior to the pin prick. The difference between *i* and *ii*, *iii* is clear.

In Fig. 5, *iv* is shown the pattern produced by aconite, on the same position. It will be seen that the manually induced single ectopic beat of Fig. 5, *i* is quite similar in form to the repetitive aconite-induced pattern of 5, *iv*. Fig. 5, *v* and *vi* show the effect of placing a potassium chloride pledget on the left ventricular apical region, after the aconite. The repetitive pattern demonstrated is similar in form to the single pattern of Fig. 5, *ii* and *iii*, an ectopic beat induced manually in a KCl affected region. There is an amplitude difference.

Thus two unrelated procedures applied together in first one order and then reversed order give rise to similar (though not identical) effects in the case of the two orders of application. Linear differences in the spatial magnitude curves can be readily studied. It is clear that a transformation giving rise to a single time-variant parameter has some advantages in detailed study of the ventricular activation process.

D. *Authenticity of Observations.*—The computing apparatus was checked at various stages during each experiment, and each unit was operating precisely

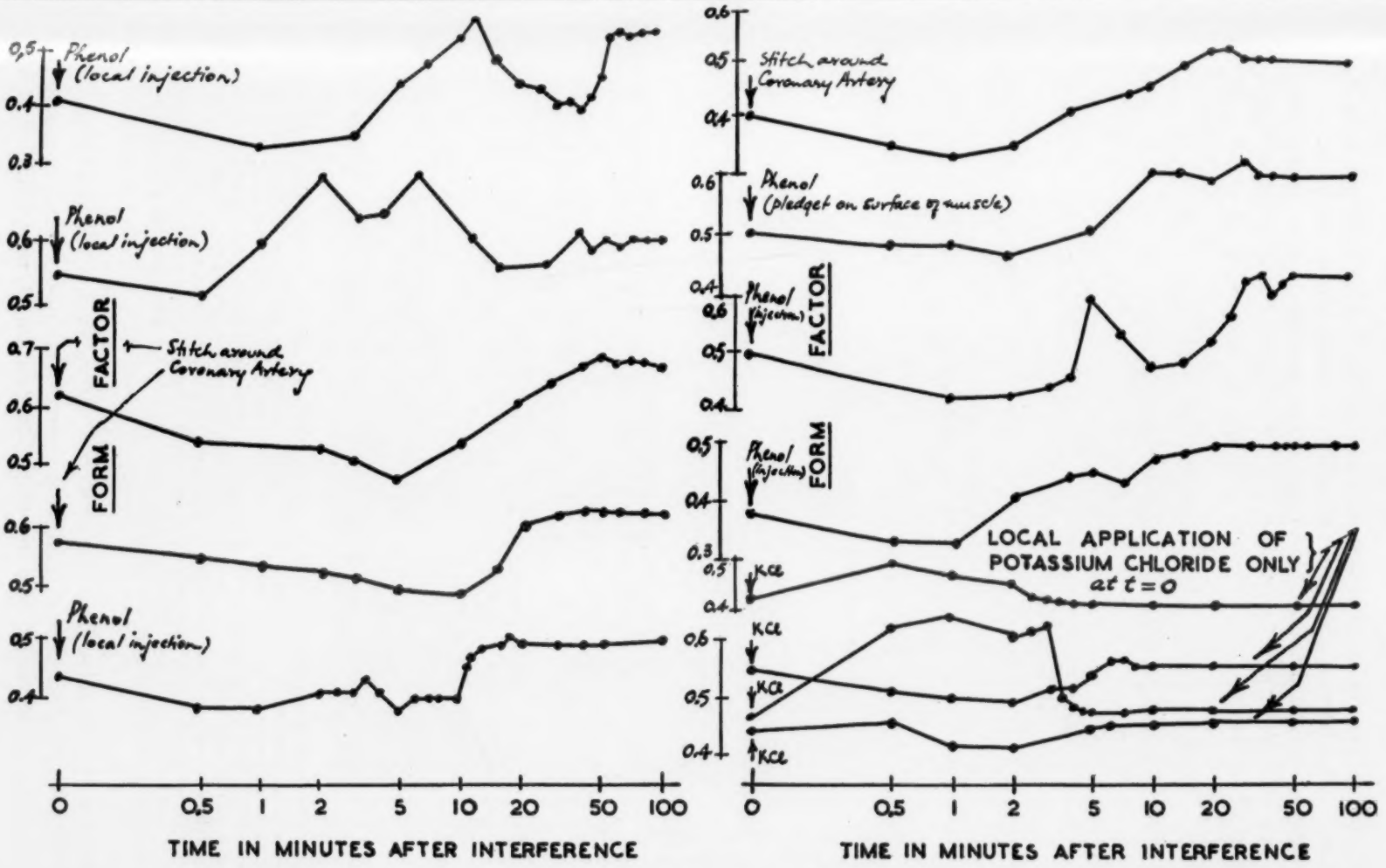

Fig. 4.—The Form Factor as a function of time. These curves show in 13 cases the effect of direct interference with the polarizing properties of cardiac muscle, using the rabbit as experimental animal. The first 9 curves are from 9 animals in which muscle death (localized into specific areas of about 1 to 2 sq. mm.) was induced by direct injection of phenol or by ligation of a branch of the coronary artery. Note the irreversible change as a function of time. The last 4 curves illustrate the effect of direct local application of potassium chloride to a small area of the heart wall. The change in each case was reversible, and the Form Factor returned (after some time) to a near normal value. Note that a logarithmic time scale has been used.

as expected. There is no evidence that any of the results reported were due to artifact. An observation on the reliability of the results is available.

A few curves of human subjects have been studied in the present series. These were found to satisfy relation (1). Furthermore the irregularities occurring in 60 patients were studied on a completely different apparatus in which

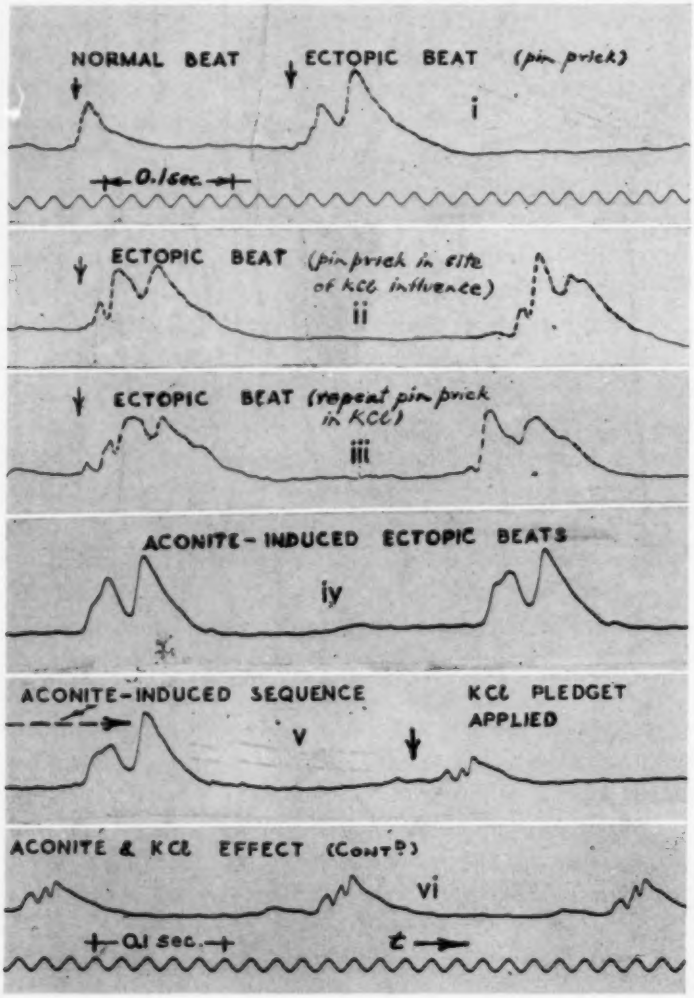

Fig. 5.—The spatial magnitude curve in the presence of ectopic beats: (The square of the curve is the function recorded here.) *i*, induced by pin prick near the left ventricular apex; *ii*, induced by pin prick at or near the same position in the site of a previous (1 minute) local depolarization induced by potassium chloride; *iii* repeat of *ii*. In *iv* the ectopic beats were induced by application of 2 per cent aconite at the same site. These ectopic beats continued for one minute until pledget, soaked in potassium chloride, was placed on the heart, at the same place. *v*, The start of the potassium chloride effect. *vi*, The similar repetitive pattern is shown, still maintained after 30 seconds under the joint influence of aconite and potassium chloride. The resemblance in shape to the single pattern of *ii* and *iii* may be noticed. The time marker is at 50 c.p.s.

the curves were calculated from vector loops. All cases in which the possibility of prolongation of QRS time existed were removed because we had no accurate time measurement available (see below). The relation (1) was found to hold,

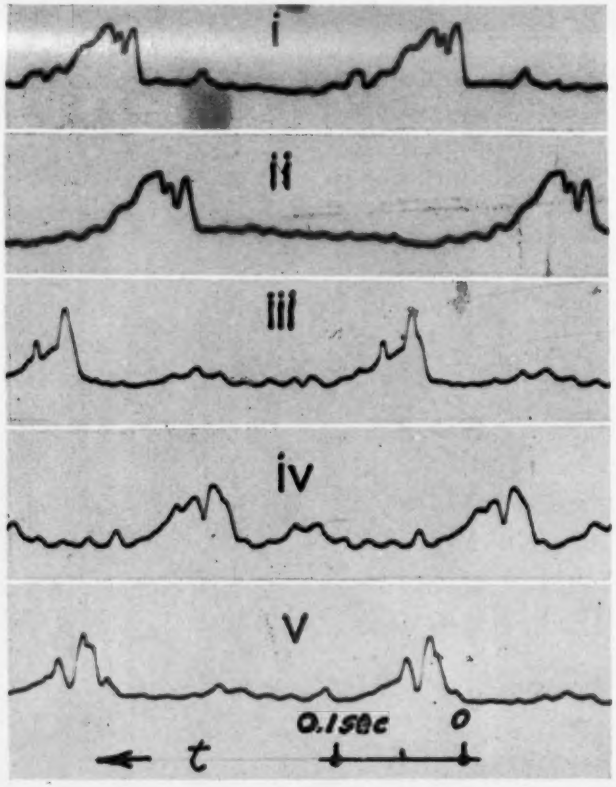

Fig. 6.

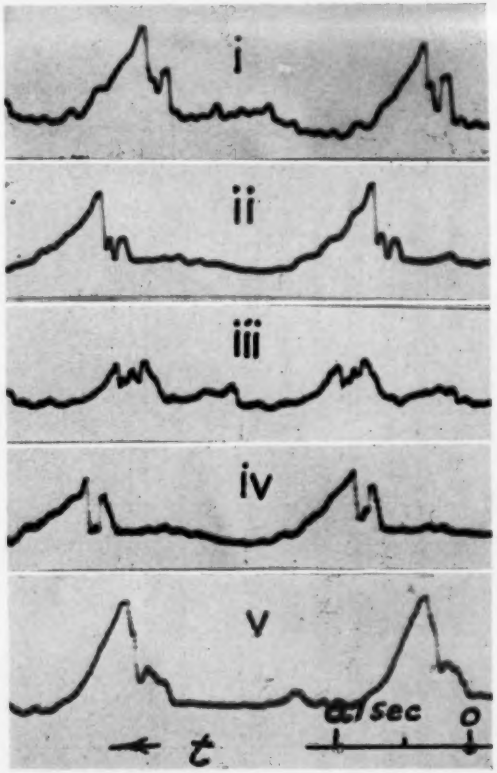

Fig. 7.

Fig. 6.—Spatial magnitude curves during phenol injection experiments—in each case the square of the curve has been recorded and the high-pass filter used had a cutoff frequency of 5 c.p.s.

The site of injection was midway apex-base, in the left ventricular wall near the septal junction; the "infarct" area was about 1 sq. mm. and involved three fourths of wall thickness.

i, Normal postoperative curve; *ii*, 10 minutes after phenol injection; *iii*, 20 minutes after injection; *iv*, 30 minutes after injection; *v*, 60 minutes after injection. The time scale (0.1 second) indicated is common to each trace.

Fig. 7.—Spatial magnitude curves as in Fig. 6; different animal. The site of injection: anterior wall left ventricle 1 cm. from apex at junction with septum; the "infarct" was 1.5 sq. mm. area and involved full thickness of the wall. *i*, Normal postoperative curve; *ii*, 1 minute after injection of phenol; *iii*, 2 minutes after injection of phenol; *iv*, 7 minutes after injection of phenol; *v*, 20 minutes after injection of phenol.

with constant "k" = 1.41 ± 0.29 over 60 cases, agreeing adequately with the value of 1.37 found for relation (1) in the present report. The lack of absolute time measurements accurately defining the instant of starting, meant that neither the value of "c" nor the starting time could be accurately assessed. Hence cases in which considerable elongation of the curve might occur would be inadequately specified. The latter cases were handled separately; assuming "c" = 0; "k" = 1.6 over 32 cases. This included every case available to us from several sources.

It must be emphasized that the relation (1) is one determined from statistical analysis of the data and may not be exactly verified in each individual "peak-minimum" pair.

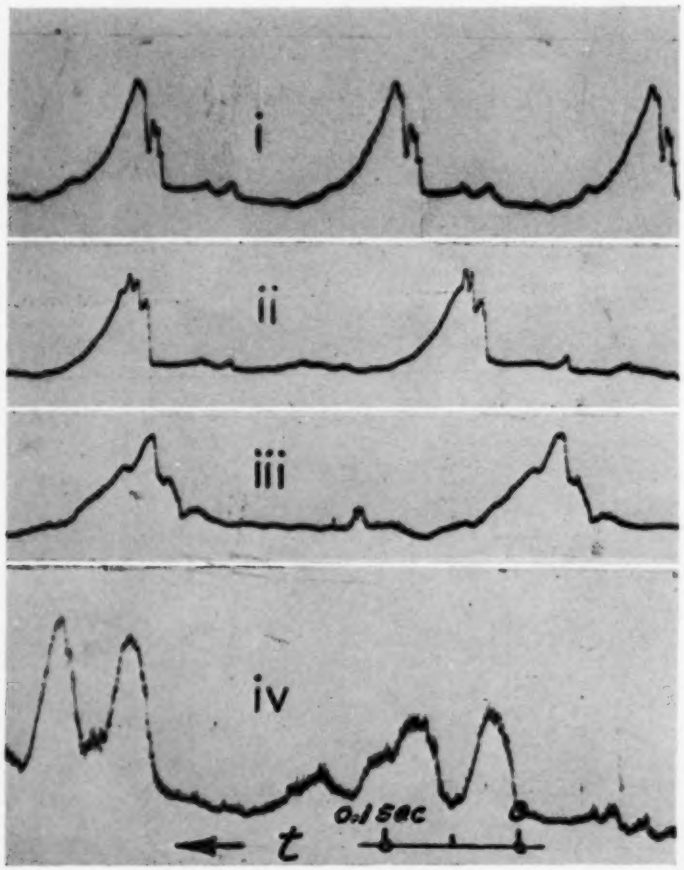

Fig. 8.—Spatial magnitude curve as in Figs. 6 and 7; different animal. The phenol spread superficially and involved the superficial muscle layer to the extent of the anterior two-third of left ventricle. A full muscle thickness "infarct" of 3 sq. mm. area was also observed. *i*, Normal postoperative curve; *ii*, 10 minutes after phenol injection; *iii*, 30 minutes after phenol injection; *iv*, 35 minutes after phenol injection—ventricular fibrillation appearing.

DISCUSSION

We have reported here some observations on several phenomena associated with the presence of high-frequency components in the spatial magnitude electrocardiogram. In an earlier paper[1] it was reported that in the case of the

human heart, a correlation existed between the times of occurrence of peaks and minima, for the gross irregularities studied there. A correlation coefficient of r = 0.79 led us with closer study to prescribe a linear relation between the two quantities.

The present investigation has verified, in the case of the rabbit heart, not only that a similar relation holds for a considerable percentage of the peak-minima pairs studied, but that it also applies to relatively high-frequency components of the spatial magnitude electrocardiogram. Furthermore, some of the irregularities appear to be altered considerably but selectively by interfering procedures. The possibility exists that the results from procedures such as phenol-induced damage of the myocardium may indicate a rough relationship between the location of the site of injury and the particular irregularities most affected.

We wish to draw attention to two features of these observations. First, a relationship of the form quoted appears to hold for both human and rabbit hearts, at least for a considerable proportion of peak-minimum pairs. Second, the relation appears to be of similar form in the case of gross irregularities, and in those in which the peak is clearly defined by components of relatively fast rise time. Taking these two observations together, it is clearly suggestive that these observations describe a phenomenon of a fundamental nature. We have not hitherto considered the implications of the relation and the subsequent suggestion, but we propose to do so now. There is some evidence of a grouping of peaks along the absolute time axis. (If this is verified there may be, of course, no direct relation between this observation and that relating the time of occurrence of peaks and minima.)

One possible implication of the observations is the presence of rapid electric vectors which may start in clearly defined temporal zones within the QRS complex. Such vectors may be described, on the basis of relation (1), as having durations linearly proportional to their times of starting. Alternatively in the case of the higher-frequency components the initial pulse, which defines the occurrence of the peak, may be better considered as isolated from the rest of the vector defined between the initial peak pulse and that indicating the end of the critical interval (t_p, t_m).

There have been other reports of such high-speed vectors. For instance, Grant[4,5] distinguishes in some cases three mean vectors representing the sum of the activation process in the first 0.02, 0.04, and 0.08 second of the human QRS complex. Penaloza and Tranchesi[6] observed the presence in the human QRS complex of three main deflections whose peaks corresponded to three main directional changes of the spatial vector loop. Goldberg and Ashman[7] and Ashman[8] have considered that in the human ventricular activation process there are six instantaneous spatial vectors.

In our series of human patients (previously reported) we have insufficient numbers on which to base a distribution survey. Indeed in most of these cases some of the high-frequency components were suppressed by the apparatus used. However, our results do indicate the presence of various rapid vectors in the QRS complex of the spatial magnitude electrocardiogram of the human heart, though the grouping of occurrence times within the complex is not clearly defined beyond reasonable doubt.

It is clear that the irregularities in the spatial magnitude curve are descriptive of modifications in the steady progress of the depolarization process. It is possible that the irregularities may correspond to the passage of the wave of depolarization into a new region of musculature in the case of each of the initial peaks, and of the cessation of the interaction currents between that region and others in the case of the minimum.

Clarification may be achieved by closer study of relation (1). Let us define Δt_p, the extension of the interval $(0, t_p)$ by the expression

$$t_p + \Delta t_p = t_m$$

Then relation (1) may be expressed

$$\frac{\Delta t_p - c}{t_p} = K\text{-}1 = \text{constant} \text{ - - - - } (2)$$

Hence the extension Δt_p varies with the starting point t_p subject to the limitation that Δt_p can never be less than c. (It is interesting to note that an expression of this form occurs widely throughout biophysics.)

The way is now clear to deduce that the duration of the irregularity under consideration is proportional to the time of first appearance and hence generally to the amount of depolarization which has preceded it. (If this deduction is correct, then the rise time of the initial peak should be independent of the duration of the irregularity.)

It is plausible to suggest that the peaks and minima described correspond, respectively, to the initial pulse of depolarization as the wave of depolarization moves into a new region and to the cessation of interaction currents between that region and other appropriate regions. In these terms, the relation (1) is not so very surprising.

With respect to the other observations concerned with variations in Form Factor and the pattern of the curve during ectopic beats little need be said. It is clear that interesting results may be obtained. It might well be that the present method of transformation offers possibilities as a research tool for investigating the ventricular activation process. We wish mainly to draw attention to some of the properties of this transformation. Perhaps the most important is that some transformation of three-dimensional information is presented in the spatial magnitude curve as a single time-varying parameter.

SUMMARY

1. Further studies of a new transformation method for studying the cardiac ventricular activation process have been reported. The present experiments have been limited to the rabbit heart.

2. Verification has been found of what appears to be perhaps a basic relation between time of occurrence of local maxima in the spatial magnitude electrocardiographic curve and the time of occurrence of subsequent minima. It has been suggested that the duration of an irregularity, so defined, in the spatial magnitude curve may be related to the amount of depolarization which preceded it. The relation has been verified only as a statistical property.

3. Evidence (further to that previously reported for human patients) suggests that for cardiac muscle death produced experimentally in the rabbit heart, the Form Factor undergoes an irreversible increase in magnitude. This supports the evidence from previous observations upon the course of the Form Factor in cases of myocardial infarction in the human heart.

4. Procedures which induce local reversible alterations in the polarizing properties of cardiac muscle (such as the local application of potassium chloride), have been shown to produce a reversible change in the Form Factor.

5. The single time-dependent parameter which specifies the spatial magnitude electrocardiogram has been shown to possess interesting properties in the study of the ventricular activation process.

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RESPONSE TO PSYCHOLOGICAL STRESS IN PATIENTS WITH ESSENTIAL HYPERTENSION

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PICKERING[1] recently reviewed the literature regarding psychological influences on the development of essential hypertension, calling such influences "environmental factors that operate through the mind." He stated that there is nothing "inherently improbable" in the notion that such factors are important, but that there is nothing conclusive about the evidence, and that much of what has been asserted regarding the psychogenesis of hypertension consists of ideas that operate through the mind of the observer, rather than the mind of the patient.

In a program of psychological research on hypertension we have utilized methods which control such error on the part of the observer. To insure that the findings cannot be attributed to incidental or secondary effects of the disease itself, we have studied young adults with elevated blood pressure. We demonstrated previously that college women with at least transiently elevated pressures (greater than 140 systolic and/or 90 diastolic) are more impulsive, more egocentric, and in general less effective in emotion-provoking situations than are appropriately matched controls with lower pressures.[2] A follow-up study of these women indicates that the personality differences still obtain after 4 years, despite the use of different methods and different observers. Such consistent findings lend weight to the inference that the women with higher pressures are likely to experience anxiety in many real-life situations and to be subject to the autonomic accompaniments of emotion, including repetitive rises of blood pressure.

The relevance of this approach to the problem of essential hypertension rests on the evidence that young adults with elevated blood pressure are prehypertensive, i.e., likely to become hypertensive in later life.[3-5] The evidence that these particular women are prehypertensive is only presumptive, and a 20-year follow-up will be required to establish that the incidence of hypertension is higher than normal in this group. Short of such extended studies, it would be of interest to establish whether the pattern of response characteristic of these prehypertensive women is like that of patients with essential hypertension. The

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present study was designed to explore two questions: (1) Do patients with essential hypertension respond in characteristic ways to laboratory-contrived, stressful situations? (2) Is their pattern of response similar to that observed in the prehypertensives?

SUBJECTS AND METHOD

Experimental subjects were 14 female hypertensive patients with slight or no vascular complications. Their diagnosis had been established by repeated examinations at the University of California Hypertension Clinic, and their average casual blood pressure at the time of the present study was 172/107 mm. Hg. Controls were 22 working women and female students who were not being treated for any illness; their average casual blood pressure was 119/73 mm. Hg.

Stress was induced experimentally by staging interpersonal situations, or psychodramas, similar to those used in the study of college women. Each subject, in turn, was assigned a role and given the synopsis of an incomplete plot which she was asked to act out with a staff member, a professional actress, who played a "standard role." The actress skillfully involved the subjects in the interactions, highlighted the conflicts, and when necessary pressed for resolution of the problem.

In the first of the two psychodramas, the subject was informed that expenses occasioned by family illness had caused her to call upon a friend who had borrowed money some time ago and failed to repay it. The staff member, who played the "friend," complicated the interaction by professing inability to repay the money and commenting that she had recently taken a vacation trip and purchased a new television set. She suggested that the subject put off the doctor and hospital bills, protested that she hadn't told her husband about the loan at the time and couldn't do so now, etc. Her manner was calculated to be patronizing, unsympathetic, and deliberately infuriating to the subject.

In the second situation, the subject was informed that she had moved into a new neighborhood and, reversing the usual procedure, was about to call on one of her neighbors. The subject, supposedly eager to integrate herself into the community, had heard that the neighbor was a member of a local club which she would like to be invited to join. In this case the staff member, playing the neighbor, greeted the subject with comments that other neighbors had complained about her manner of dress in public, the behavior of her children, etc. The neighbor emphasized the exclusiveness of the neighborhood and, when the question was brought up, of the club.

In the first situation, the subject's task essentially was to be sufficiently assertive and counteractive to insure that the friend would agree to repay the money. In the second, her task was less well defined, but involved gaining the friendship and support of the neighbor rather than alienating her.

Two or more observers recorded their impressions of the interactions by checking 19 variables selected for their presumed relevance to blood pressure, as determined by the study of prehypertensives. These checks will be referred to as interaction variables. Subjects were also rated on five-point scales for overall effectiveness, organization and control, and participation. Another device

to record the observers' impressions was the utilization of adjectives checked as most descriptive of each subject.[6]

Typescripts transcribed from sound recordings of the psychodramas were also rated on ten scales by a staff member who had not observed the interactions. This separate analysis was introduced to permit more detailed study of the subjects' verbalizations.

RESULTS

Following the stress situations, both groups showed rises in blood pressure and heart rate. These increases were evidence that the situations were, in fact, emotion-provoking. The increases were significantly greater in the hypertensive group than in the control group (Fig. 1).

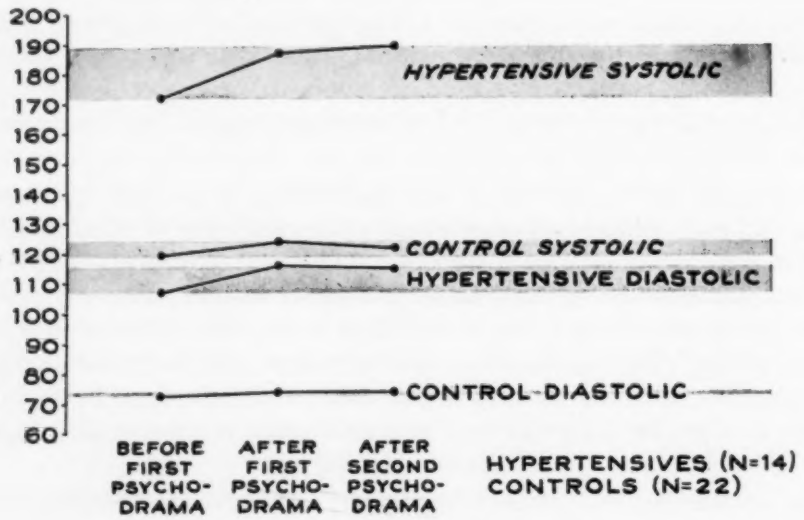

Fig. 1.—Mean blood pressure changes with psychodramatic stress.

The difference in systolic increase was significant at less than the 0.02 level of confidence, and the diastolic at less than 0.01. The hypertensive women had higher initial heart rates (a mean of 90 compared to 81 for the controls); the mean rate in this group rose to 98, while that of the control group was 83 following the first psychodrama. This difference in increment was significant at less than the 0.05 level.

OBSERVERS' IMPRESSIONS

Of the 19 interaction variables, 11 significantly separated the hypertensive patients from the controls, as shown in Table I.

The hypertensives were more self-punishing and showed more evidence of suppressing anger in both psychodramas, while the controls were more persistent in both. In the first drama the hypertensives were more often checked as appeasing, denying guilt, uncertain and confused, submissive and repetitive-persevera-

tive. The controls were checked as expressing affect more appropriately in the first drama, with a trend in this direction in the second. In the second drama, the hypertensives were hostile and attacking, and they more frequently blocked, necessitating "rescue" by the standard role player.

TABLE I. DIFFERENCES IN PSYCHODRAMA BEHAVIOR BASED ON OBSERVER CHECKS OF INTERACTION VARIABLES

VARIABLE	SUBJECTS CHECKED MORE OFTEN	DRAMA 1 p*	DRAMA 2
Both Psychodramas			
Self-punishing	Hypertensive	0.10	0.001
Suppressing anger	Hypertensive	0.05	0.10
Persisting	Control	0.01	0.05
First Psychodrama			
Appeasing	Hypertensive	0.01	
Denying guilt	Hypertensive	0.02	
Uncertain, confused	Hypertensive	0.05	
Submissive	Hypertensive	0.10	
Repetitive, perseverative	Hypertensive	0.10	
Appropriate affect	Control	0.01	
Second Psychodrama			
Hostile, attacking	Hypertensive		0.05
Blocking	Hypertensive		0.10

*Probability based on standard error of difference between proportions, two-tailed test.

On the ratings in Table II, the controls were more effective, showed more organization and control, and were more participative in the interactions, although the latter trend was not statistically significant.

TABLE II. DIFFERENCES IN PSYCHODRAMA BEHAVIOR BASED ON OBSERVER RATINGS

RATING	MEAN		SE_d	t	p*
	HYPERTENSIVES	CONTROLS			
Effectiveness	2.91	3.74	0.375	2.21	0.05
Organization and control	3.04	3.94	0.214	4.21	0.001
Participation	3.36	3.60	0.279	1.58	N.S.

*Probability based on *t*-test for standard error of difference between means, two-tailed test.

Most of these differences are virtually identical with those observed in our previous study of prehypertensive women in similar psychodramas. Moreover, analysis of the adjectives differentiating hypertensive from control patients showed that these were strikingly congruent with those differentiating the prehypertensive college women from their appropriate controls. Table III lists the adjectives which were identical for the two sets of subjects. It is apparent from these lists that the groups differ with respect to emotional control and relations

with other people. In addition, there were other discriminating adjectives which are synonymous with the words emerging from the earlier research.

TABLE III. ADJECTIVES DIFFERENTIATING BOTH PREHYPERTENSIVE WOMEN AND PATIENTS WITH ESSENTIAL HYPERTENSION FROM APPROPRIATE CONTROL GROUPS*

CHECKED MORE OFTEN FOR PREHYPERTENSIVES AND HYPERTENSIVES	CHECKED MORE OFTEN FOR APPROPRIATE CONTROLS
Emotional	Adaptable
Grave	Affectionate
Guarded	Considerate
Imprudent	Cooperative
Intense	Dependable
Nervous	Efficient
Peculiar	Even
Prudish	Kind
Resentful	Likeable
Restless	Tactful
Self-centered	
Sour	
Unsympathetic	

*Based on *t*-test for standard error of difference between proportions, two-tailed test.

RATINGS OF TYPESCRIPTS

The ratings of typescripts also differentiated the hypertensive subjects from the controls in several respects. Ten of the differences between means were significant, as shown in Table IV. The hypertensive patients were more assertive, more tense, and expressed more hostility than the controls. The latter were more flexible, strived for resolution of the problem (closure), showed better emotional control, were more task-oriented, responsive, and generally more effective than the hypertensives.

TABLE IV. DIFFERENCES IN PSYCHODRAMA BEHAVIOR BASED ON RATINGS OF TYPESCRIPTS

RATING	GROUP RATED HIGHER	DRAMA 1 P*	DRAMA 2
Plot flexibility	Control	0.01	0.01
Closure	Control	0.01	
Assertiveness	Hypertensive		0.05
Tension level	Hypertensive		0.05
Emotional control	Control	0.05	
Expressed hostility	Hypertensive		0.05
Task orientation	Control	0.05	
Responsiveness	Control		0.05
Over-all effectiveness	Control	0.05	
Poise	Control		

*Probability based on *t*-test for standard error of difference between means, two-tailed test.

The hypertensive patients were older than the controls; however, only one of the variables showed a significant correlation with age. The fact that the

others did not, together with the similarity of the findings with those of the earlier study where age was controlled, suggests that the age difference is not a critical one.

DISCUSSION

The striking similarity between the behavior patterns of these hypertensive women and the prehypertensive college women described in a previous report[2] is a link in our understanding of the emotional aspects of essential hypertension. The patients in the present study show the same characteristics found before the onset of definitive hypertensive disease; and the hypothesis that such characteristics are important in the development and course of essential hypertension is strengthened.

The findings in general support clinical psychiatric descriptions of "the hypertensive personality." Saslow and associates[7] have claimed that "subnormal assertiveness" is characteristic of hypertensives; and Saul,[8] Wolf and Wolff,[9] and others have attached importance to the suppression or repression of hostility. The data of the present study support as well as amplify the meaning of these findings. A review of the relationships between the behavior of the subjects and the implied demands of the situations is revealing. The hypertensive patients were more assertive and expressed more hostility in the second psychodrama than did the controls. It should be noted, however, that assertiveness and overtly expressed hostility were maladaptive in this situation, where tact and submission, necessary to remain in the good graces of the neighbor, could be considered optimal behavior. The hypertensive patients, then, were *inappropriate* in their assertiveness and expression of hostility. Moreover, in the first psychodrama where assertiveness and expression of hostility were called for by the nature of the task, the controls were checked more often, although not significantly so, on both these variables. It would appear, therefore, that the hypertensives were not only inappropriately assertive and hostile, but in this case, at least, their inappropriateness represented a delayed reaction.

Of importance also is the finding that the hypertensives were rated as *suppressing* more anger at the same time that they were *expressing* more anger than the controls. The adjectives checked by the observers suggest that difficulties in emotional control and relations with other people are pervasive personality problems for the subjects with prehypertension and those with essential hypertension.

SUMMARY

Thirty-six women, 14 with essential hypertension and 22 normal controls, were observed in two psychodramatic stress situations. Both blood pressure and heart rate as well as psychological response to stress differed for the two groups. Ratings based upon descriptions by observers and upon typescripts of psychodrama behavior showed that the hypertensive women had poorer emotional and behavioral control, were less flexible and adaptive in the stress situations, and lacked appropriate assertiveness. These findings are consistent with those reported in studies of prehypertensive subjects and with hypotheses regarding the behavioral correlates of hypertension which have emerged from psychiatric inter-

views. They suggest that prehypertensive as well as hypertensive subjects perceive stress more readily and handle it less well. Thus, they are more vulnerable to repetitive rises in blood pressure which may lead ultimately to essential hypertension.

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SIMULTANEOUS (COMBINED) CATHETERIZATION OF THE LEFT AND RIGHT HEART

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EVALUATION of the altered circulatory dynamics secondary to valvular lesions of the left side of the heart has, until recently, been dependent upon right heart catheterization.[1-3] Although these data were useful in mitral stenosis, these studies provided little information concerning the pathologic physiology of aortic valvular disease. With the introduction of left heart catheterization,[4,5] a method of study was made available for measurement of the pressure gradients across stenotic mitral and aortic valves. For a complete evaluation of the significance of these pressure changes, one must have knowledge of the existing flows across the valve at the moment these pressures are recorded. Hence, we have employed catheterization of the right and left heart simultaneously for the purpose of recording the pressure-flow relationships.[6] The application of this method of study to patients with mitral and aortic stenosis provides the material for this report. Three patients with normal cardiovascular systems are included. Our experiences in the first 127 consecutive left heart catheterizations are reported elsewhere.[7,8]

METHOD OF STUDY

All studies were done in the postabsorptive state. Premedication consisted of Seconal 0.2 Gm. and Demerol 50 mg. Right heart catheterization was performed in the usual way except that the patient was lying in the prone position on the fluoroscopic table. After recording the pulmonary venous "capillary" pressure, the catheter was withdrawn and positioned in the right or left pulmonary artery close to the hilus, so that it could be advanced later and wedged into the pulmonary artery. A Cournand needle was then placed into the brachial artery. The method for left heart catheterization was similar to that described previously.[7] With the aid of a preliminary 36-inch supine posteroanterior roentgenogram of the chest and fluoroscopy, selection of the intercostal space was made. A sharp 6 inch No. 18G thin-walled Becton & Dickinson needle was inserted into the left atrium. A polyethylene or nylon catheter was inserted through the needle, and advanced into the left ventricle with continuous monitoring of the pressure on the oscilloscope or polyoscillograph (Sanborn). In some patients a deliberate attempt to enter the aorta was made. As soon as the control cardiac rate, rhythm, and blood pressure were re-established cardiac output was determined by the direct Fick method. Pressures were then recorded immediately from the brachial artery and left ventricle simultaneously

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to determine the left ventricular-brachial arterial pressure gradient, and as the catheter was withdrawn from the left ventricle to the left atrium to determine the ventricular filling pressure gradient (i.e., left atrial-left ventricular gradient). In three patients with mitral stenosis and atrial fibrillation, a second needle was inserted into the left atrium and simultaneous recordings made from the left atrium and left ventricle during the determination of the cardiac output.

Pressure gradients were calculated by planimetric integration (Figs. 1 and 2). Valve area and pulmonary resistance were calculated by modification of the formulae of Gorlin and Gorlin[9] and ventricular work as originally proposed.

Mitral Valve Area.—

$$M.V.A.\ (\text{cm.}^2) = \frac{M.V.F.}{31\sqrt{V.F.G.}}$$

$$M.V.F.\ (\text{c.c./}V.F.P.\ \text{sec.}) = \frac{C.O.\ (\text{c.c./min.})}{V.F.P. \times H.R.}$$

$$V.F.G.\ (\text{mm. Hg}) = L.A._{v.f.p.} - L.V._{v.f.p.} \quad \text{(Fig. 1)}$$

Aortic Valve Area.—

$$A.V.A.\ (\text{cm.}^2) = \frac{A.V.F.}{44.5\sqrt{S.P.G.}}$$

$$A.V.F.\ (\text{c.c./}S.E.P.\ \text{sec.}) = \frac{C.O.\ (\text{c.c./min.})}{S.E.P. \times H.R.}$$

$$S.P.G.\ (\text{mm. Hg}) = L.V._{m.s.} - B.A._{m.s.} \quad \text{(Fig. 2)}$$

Pulmonary Vascular Resistance.—

$$P.V.R.\ (\text{dynes sec./cm.}^{-5}) = \frac{(P.A._m. - L.A._m.) \times 1332}{C.O.\ (\text{c.c./sec.})}$$

Abbreviations.—

$M.V.A.$	=	Mitral valve area,
$M.V.F.$	=	Mitral valve flow,
$V.F.G.$	=	Ventricular filling pressure gradient (Fig. 1),
$V.F.P.$	=	Ventricular filling period (Fig. 1),
$H.R.$	=	Heart rate,
$L.A._{v.f.p.}$	=	Mean left atrial pressure during ventricular filling period,
$L.V._{v.f.p.}$	=	Mean left ventricular pressure during ventricular filling period,
$C.O.$	=	Cardiac output,
$A.V.A.$	=	Aortic valve area,
$A.V.F.$	=	Aortic valve flow,
$S.P.G.$	=	Systolic pressure gradient (Fig. 2),
$S.E.P.$	=	Systolic ejection period (Fig. 2),
$L.V._{m.s.}$	=	Mean left ventricular systolic ejection pressure,
$B.A._{m.s.}$	=	Mean brachial artery systolic pressure,
$P.V.R.$	=	Pulmonary vascular resistance,
$P.A._m.$	=	Mean pulmonary artery pressure, and
$L.A._m$	=	Mean left atrial pressure.

MATERIAL

Three groups of patients were studied. Group 1 consisted of three patients with normal cardiovascular systems as revealed by history, physical exami-

nation, x-ray, and electrocardiogram. Group 2 comprised twelve patients with pure mitral stenosis. This diagnosis was confirmed at surgery in all. Four patients were re-evaluated fourteen days after mitral commissurotomy. Group 3 consisted of eleven patients with pure aortic stenosis. The diagnosis was confirmed at surgery in ten cases and at autopsy in one. Three patients were re-evaluated fourteen days following aortic commissurotomy.

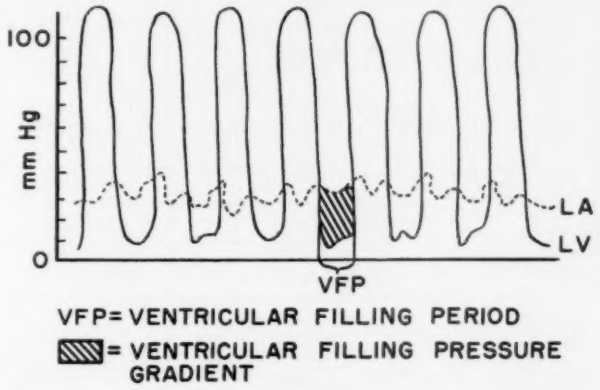


Fig. 1.—Mitral stenosis: Left ventricular (solid line) and left atrial (dotted line) pressure tracings redrawn and superimposed. *V.F.P.* is ventricular filling period. Shaded area represents ventricular filling pressure gradient.

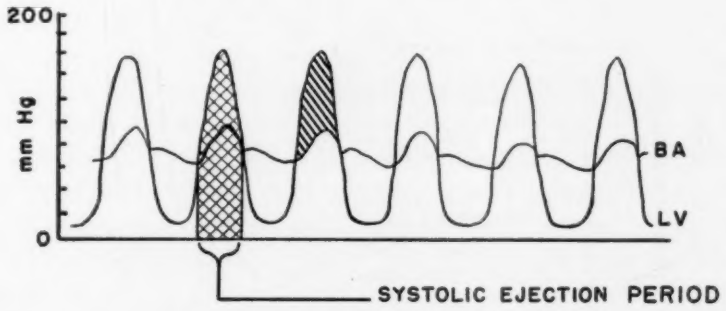


Fig. 2.—Aortic stenosis: Brachial artery (*B.A.*) and left ventricular (*L.V.*) pressure tracings redrawn and superimposed. Note systolic pressure gradient (cross hatched) and systolic ejection pressure (double cross hatched). The systolic ejection period is indicated.

RESULTS

GROUP 1.—

Cardiovascular Normal Subjects.—The data obtained in the three patients in this group are shown in Table I. The mitral valve flows were 138, 248, and 156 c.c./V.F.P. sec. and the aortic valve flows were 228, 231, and 175 c.c./S.E.P. sec.

The end-diastolic pressure in the left ventricle and the mean left atrial pressures were below 10 mm. Hg in all. The left atrial pressure curve consisted of three positive waves, a, c, and v, and a negative wave, x, between the c and v waves.

TABLE I. NORMAL SUBJECTS

PATIENT	BODY SURFACE AREA ($M.^2$BS)	OXYGEN CONSUMPTION (C.C./MIN.)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. %)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./$M.^2$BS)	HEART RATE (BEATS/MIN.)	STROKE VOLUME (C.C./BEAT)	PULMONIC CIRCULATION						SYSTEMIC CIRCULATION												
								PRESSURES (mm. Hg)				PULMONARY VASCULAR RESISTANCE (DYNES SEC./CM.$^{-5}$)	RIGHT VENTRICULAR WORK (KG.M./MIN.)	PRESSURES (mm. Hg)											
								RIGHT ATRIUM (MEAN)	RIGHT VENTRICLE (S/D)	PULMONARY ARTERY (S/D) (MEAN)	PULMONARY "CAPILLARY" (MEAN)			LEFT ATRIUM (MEAN)	LEFT VENTRICLE (S/D)	AORTA (S/D) (MEAN)	BRACHIAL ARTERY (S/D) (MEAN)	LEFT VENTRICULAR EJECTION (MEAN)	VENTRICULAR FILLING PRESSURE GRADIENT*	MITRAL VALVE FLOW (C.C./V.P.P. SEC.)	LEFT VENTRICULAR FILLING PERIOD (SEC./MIN.)	MITRAL VALVE AREA ($CM.^2$)	SYSTOLIC EJECTION PERIOD (SEC.)	AORTIC VALVE FLOW (C.C./S.E.P. SEC.)	AORTIC VALVE AREA ($CM.^2$)	LEFT VENTRICULAR WORK, TOTAL (KG.M./MIN.)
V.Y.	1.66	174	3.6	4.8	2.9	88	55	2	22 — 4	20 — (11) 9	8	100	0.44	5	90 — 4	100 — (84) 70	105 — (80) 60	78	0	138	35	—	0.24	228	—	3.25
B.Y.	1.35	184	4.7	5.0	3.7	120	42	0	14 — 2	12 — (10) 6	—	127	0.53	5	105 — 4	—	128 — (90) 80	—	0	248	20	—	0.18	231	—	—
M.R.	1.66	160	3.8	4.2	2.5	81	52	4	27 — 4	21 — (19) 11	5	228	0.68	7	114 — 7	114 — (92) 76	116 — (90) 70	112	0	156	27	—	0.28	185	—	3.98

*Measured by planimetric integration.

There was no measurable pressure gradient between the left atrium and left ventricle during ventricular diastole. Similarly, there was no measurable pressure gradient between the left ventricle and aorta during ventricular systole (Patient V.Y.). Negative pressure gradients of 2, 15, and 23 mm. Hg existed between the left ventricle and brachial artery during systole.

In the absence of measurable pressure gradients across the mitral and aortic valve, the orifice sizes could not be calculated from the hydraulic formulae employed.

GROUP 2.—

Mitral Stenosis—Preoperative Studies.—The data obtained from right heart catheterization were similar to those reported previously[1,2] and are shown in Table II,*A*. The cardiac index tended to be low for the group as a whole, averaging 2.1 L./min./M.^{2} (range: 1.1 to 4.5 L./min./M.^{2}). In those individuals in whom the index was reduced, the arteriovenous oxygen difference was increased.

The mean pulmonary artery pressure was elevated in all patients but one. The pulmonary "capillary" and left atrial pressures were similar in magnitude and generally elevated. Although the "capillary" pressure curve had more artefacts, there was generally good agreement between the left atrial and "capillary" pressure tracings in contour.

The end-diastolic pressure in the left ventricle was 10 mm. Hg or below in all cases but one.

A pressure gradient during left ventricular filling (V.F.G.) was constantly observed (Fig. 1) and ranged between 9 and 25 mm. Hg. The mitral valve flows were generally reduced, ranging between 61 and 190 c.c./V.F.P. sec. The mitral valve areas were reduced below normal, ranging between 0.5 and 1.3 cm.^{2}.

The effective work of the right ventricle was increased (greater than 1.0 Kg.M./min.) in six cases and within normal limits in six. The cardiac index was reduced in all of the latter group. The pulmonary vascular resistance was elevated generally.

Mitral Stenosis—Postoperative Studies.—Four patients were studied fourteen days following mitral commissurotomy. The data are shown in Table II,*B*.

The cardiac output increased and the arteriovenous oxygen difference fell in three patients. The pulmonary artery pressure decreased significantly in two patients. The work of the right ventricle decreased in two, rose slightly in one, and remained within normal limits in one. The left atrial pressure decreased in three patients. In the fourth, in whom the left atrial pressure was unchanged, the left ventricular end-diastolic pressure rose. There was a significant fall in the left ventricular filling pressure gradient in all four patients (Fig. 3). The mitral valve flows and areas increased significantly in all.

The ventricular filling period decreased in all the patients. This was considered a significant change in three cases, two of which had similar heart rates during both pre- and postoperative studies, and a third in which the rate was slower at the time of the second catheterization. In the fourth patient, shorten-

TABLE II

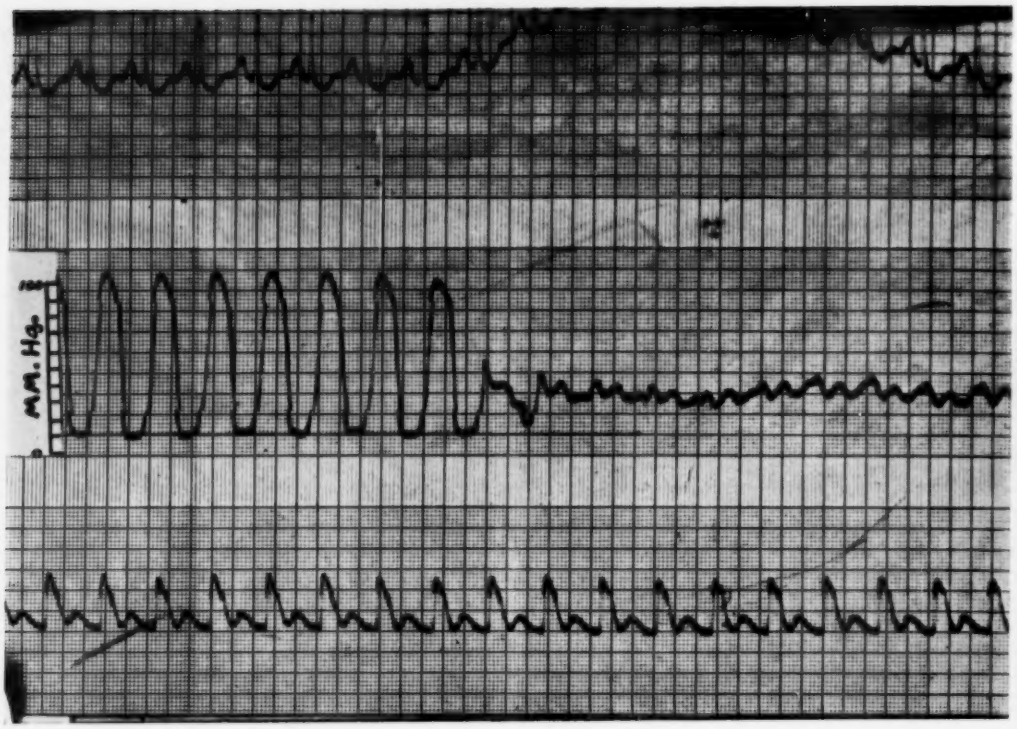
PATIENT	BODY SURFACE AREA ($M.^2$BS)	OXYGEN CONSUMPTION (C.C./MIN.)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. %)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./$M.^2$BS)	HEART RATE (BEATS/MIN.)	STROKE VOLUME (C.C./BEAT)	PULMONIC CIRCULATION						SYSTEMIC CIRCULATION									
								PRESSURES (mm. Hg)						PRESSURES (mm. Hg)									
								RIGHT ATRIUM (MEAN)	RIGHT VENTRICLE (S/D)	PULMONARY ARTERY (S/D) (MEAN)	PULMONARY CAPILLARY (MEAN)	PULMONARY VASCULAR RESISTANCE (DYNES. SEC./$CM.^{-5}$)	RIGHT VENTRICULAR WORK (Kg.M./MIN.)	LEFT ATRIUM (MEAN)	LEFT VENTRICLE (S/D)	AORTA (S/D) (MEAN)	BRACHIAL ARTERY (S/D) (MEAN)	LEFT VENTRICULAR SYSTOLIC EJECTION (MEAN)	LEFT VENTRICULAR EJECTION PERIOD (SEC.)	LEFT VENTRICULAR FILLING PERIOD (SEC./MIN.)	LEFT VENTRICULAR WORK EFFECTIVE (Kg.M./MIN.)	VENTRICULAR FILLING PRESSURE GRADIENT* (mm. Hg)	MITRAL VALVE FLOW (C.C./V.F.P. SEC.)	MITRAL VALVE AREA ($CM.^2$)
A. Mitral Stenosis																							
A.V.	1.65	187	10.2	1.8	1.1	92	20	—	—	31/20 (24)	20	178	0.38	20	103/10	—	125/82 (96)	91	.22	26	1.52	10	70	0.7
L.S.	1.55	232	8.2	2.8	1.8	121	23	19	120/10	112/60 (85)	37	1310	2.20	39	95/6	—	107/65 (74)	88	.20	34	1.91	21	82	0.5
H.D.	1.92	191	8.3	2.3	1.2	85	27	11	58/20	62/36 (40)	—	661	0.69	21	102/8	126/110	120/80 (100)	78	.18	34	1.72	9	68	0.7
M.F.	1.57	187	5.6	3.3	2.1	110	30	0	58/4	62/48 (59)	32	703	1.78	30	120/8	—	118/70 (90)	100	.28	32	2.7	25	104	0.7
A.S.	1.57	182	5.1	3.6	2.3	100	36	0	65/5	62/40 (50)	26	511	1.65	27	98/7	—	98/60 (80)	80	.14	28	2.60	14	129	1.1
I.G.	1.40	189	3.0	6.3	4.5	118	53	7	62/4	60/30 (41)	32	203	2.65	25	115/4	—	118/62 (75)	—	.16	34	4.83	24	190	1.3
A.F.	1.56	230	5.8	4.0	2.6	102	39	3	29	30	14	49	0.75	10	87	107								

A.F.	1.56	230	5.8	4.0	2.6	102	39	3	29/8	30/15 (20)	14	40	0.75	18	97/8	107/72 (76)	123/89 (100)	89	.18	31	3.73	13	130	1.2
H.P.	1.64	202	8.9	2.3	1.4	99	23	—	—	50/25 (40)	21	522	0.80	25	124/18	—	126/76 (102)	115	.24	38	2.05	12	61	0.6

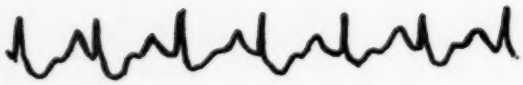
B. Mitral Stenosis—Before and After Mitral Commissurotomy

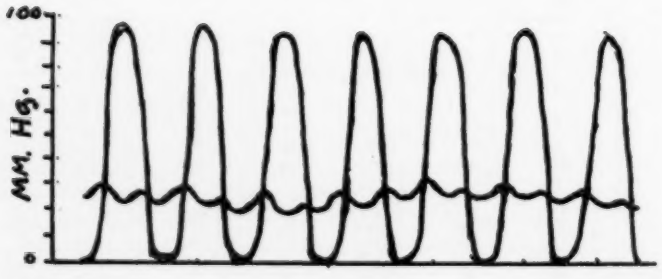
H.M. Preop.	1.76	205	4.6	4.4	2.5	108	41	0	20/0	23/12 (18)	12	127	0.65	11	92/0	98/46 (77)	116/76 (80)	84	.20	30	2.9	15	145	1.2
Postop.	1.68	217	3.4	6.4	3.8	108	59	—	—	20/8 (11)	10	13	0.60	10	94/9	—	105/52 (80)	80	.21	22	4.36	5	296	4.3
D.M. Preop.	1.53	156	5.3	2.6	1.7	80	33	—	—	50/20 (30)	19	368	0.73	18	94/4	96/60 (70)	106/68 (80)	70	.20	30	1.95	12	87	0.8
Postop.	1.48	172	5.0	3.4	2.3	110	31	0	44/2	46/23 (30)	10	425	1.0	12	100/6	—	120/64 (84)	96	.20	22	2.78	5	155	2.3
M.S. Preop.	1.57	164	4.6	3.6	2.3	123	29	10	—	45/28 (35)	28	200	1.15	26	94/5	110/68 (85)	114/60 (70)	77	.24	29	2.31	19	122	0.9
Postop.	1.54	164	3.3	5.0	3.2	127	39	—	—	30/15 (20)	13	160	0.92	10	108/5	100/70 (90)	110/80 (90)	102	.26	21	4.13	6	234	3.2
C.M. Preop.	1.70	232	6.0	3.9	2.3	114	34	5	53/5	50/35 (40)	22	308	1.32	25	96/0	—	130/70 (100)	86	.16	27	3.3	20	125	0.8
Postop.	1.65	170	4.5	3.8	2.3	100	38	0	20/0	18/5 (10)	3	42	0.33	8	103/8	—	—	—	—	17	—	4	226	3.6

*Measured by planimetric integration.



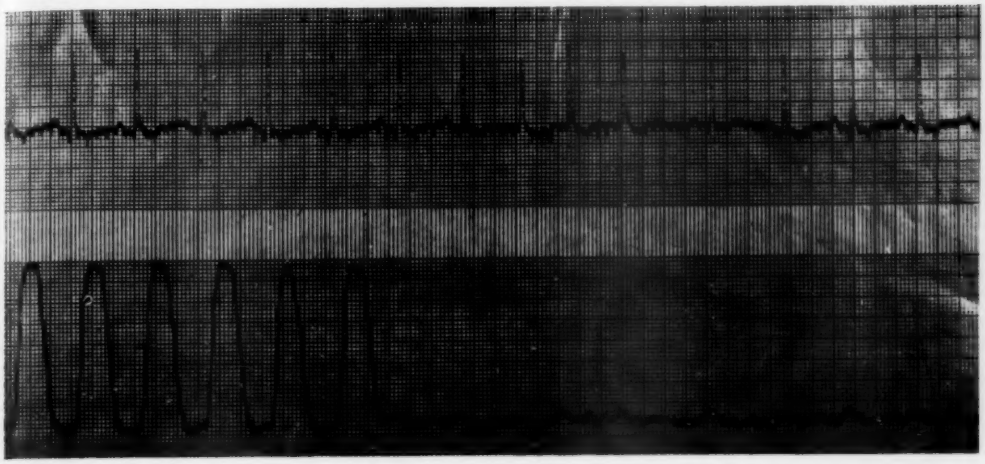
3, *A*.



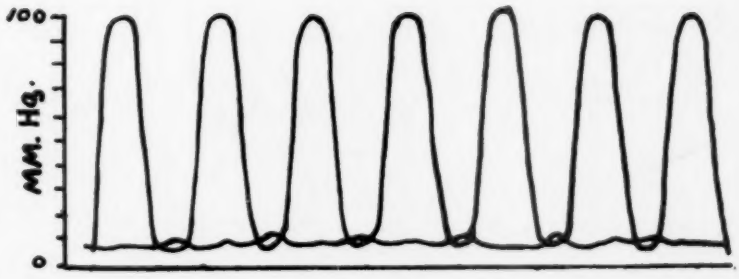


3, *B*.

Fig. 3.—Mitral stenosis (Patient M.S.): *A*, Preoperatively. Continuous pressures recorded from the left ventricle to left atrium (middle). ECG above and brachial artery pressure tracing below. *B*, Same as *A*. Left atrial and ventricular pressure tracings redrawn and superimposed showing pressure gradient. Mitral valve area — 0.8 cm.². *C*, Same patient, postmitral commissurotomy. Note lower left atrial pressure. *D*, Same as *B*. Note decrease in pressure gradient. Mitral valve area —3.6 cm.².



3, *C.*



3, *D.*

ing of the ventricular filling period may be due in part to the increase in heart rate postoperatively.

GROUP 3.—

Aortic Stenosis—Preoperative.—The physiologic data obtained in patients of Group 3 are shown in Table III,*A*. In general, the data obtained from right heart catheterization were similar to those reported previously.[3] The cardiac index was generally low for this group, averaging 2.0 L./min./M.^{2} (range: 1.0 to 2.7).

TABLE III

PATIENT	BODY SURFACE AREA ($M.^2$BS)	OXYGEN CONSUMPTION (C.C./MIN.)	ARTERIOVENOUS OXYGEN DIFFERENCE (VOL. %)	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX (L./MIN./$M.^2$BS)	HEART RATE (BEATS/MIN.)	STROKE VOLUME (C.C./BEAT)	PULMONIC CIRCULATION							SYSTEMIC CIRCULATION									
								PRESSURES (mm. Hg)							PRESSURES (mm. Hg)									
								RIGHT ATRIUM (MEAN)	RIGHT VENTRICLE (S/D)	PULMONARY ARTERY (S/D) (MEAN)	PULMONARY CAPILLARY (MEAN)	PULMONARY VASCULAR RESISTANCE (DYNES SEC./CM.$^{-5}$)	RIGHT VENTRICULAR WORK (KG.M./MIN.)		LEFT ATRIUM (MEAN)	LEFT VENTRICLE (S/D)	AORTA (S/D) (MEAN)	BRACHIAL ARTERY (S/D) (MEAN)	VENTRICULAR FILLING PRESSURE GRADIENT**	LEFT VENTRICULAR EJECTION (MEAN)	SYSTOLIC EJECTION PERIOD (SEC.)	L.V.–B.A. GRADIENT (MM. HG)*	AORTIC VALVE FLOW (C.C./S.E.P. SEC.)	AORTIC VALVE AREA ($CM.^2$)	LEFT VENTRICULAR WORK, EFFECTIVE (KG.M./MIN.)	LEFT VENTRICULAR WORK, TOTAL (KG.M./MIN.)
A. Aortic Stenosis																										
A.G.	1.49	155	4.5	3.4	2.3	64	53	11	—	30 — (20) 14	—	182	0.66		10	188 — — 18	—	110 — (86) — 80	N.M. **	165	.28	67	128	0.4	2.85	5.45 *
S.H.	1.93	233	4.4	5.3	2.7	68	78	0	29 — — 4	28 — (15) — 10	5	91	0.58		9	180 — — 16	—	134 — (100) — 80	N.M.	169	.24	46	243	0.8	3.86	6.55
S.B.	1.80	310	7.1	4.4	2.4	67	66	5	45 — — 7	42 — (32) — 19	—	144	0.81		24	150 — — 24	104 — (86) — 78	104 — (80) — 70	N.M.	138	.32	25	206	0.9	2.99	4.80
S.Be.	1.62	208	5.3	3.9	2.4	90	44	9	39 — — 8	30 — (20) — 15	9	249	0.69		8	232 — — 20	140 — (100) — 78	140 — (105) — 82	N.M.	193	.24	57	193	0.5	3.61	6.65
J.B.	1.93	209	7.2	2.9	1.5	86	34	—	—	35 — (20) — 15	—	22	0.43		12	170 — — 16	100 — (82) — 74	100 — (80) — 70	N.M.	153	.32	59	104	0.3	1.77	3.32
S.F.	1.78	197	4.7	4.2	2.4	95	44	0	20 — — 5	21 — (15) — 10	8	114	0.38		9	230 — — 7	110 — (86) — 78	120 — (84) — 72	N.M.	177	.27	74	159	0.4	2.69	6.10

J.H.	1.73	256	9.4	2.6	1.5	124	21	6	75/— 8	74/— (55) 45	20	1050	0.91	22	170/— 28	108/— (74) 60	108/— (88) 74	N.M.	142	.28	60	81	0.2	1.90 ***	3.06
J.S.	2.00	211	10.4	2.0	1.0	78	26	—	30-50/— — 5-10	30-40/— — (29) 15-20	10	759	0.42	10	104-160/— — 12- 14	—	96-124/— — (78) 56-70	N.M.	125	.22	28	116	0.5	1.12	1.80

B. Aortic Stenosis—Before and After Aortic Commissurotomy

M.M. Preop.	1.75	186	5.5	3.4	1.9	85	40	—	—	32/— (25) 18	11	235	0.68	15	190/— 20	120/— (105) 90	140/— (110) 100	N.M.	179	.26	43	143	0.5	3.00	4.90
Postop.	1.72	183	5.3	3.4	2.0	105	33	8	23/— 8	27/— (18) 12	9	141	0.52	12	102/— 18	102/— (90) 80	104/— (92) 76	N.M.	95	.20	0	162	—	2.64	2.72
C.McD. Preop.	1.81	211	6.6	3.2	1.8	76	42	4	27/— 4	25/— (22) 10	11	274	0.92	11	210/— 26	140/— (98) 80	142/— (94) 80	N.M.	165	.32	55	131	0.4	2.4	4.30
Postop.	1.57	235	5.3	4.4	2.8	75	59	10	—	40/— (30) 20	15	182	1.1	20	196/— 20	—	120/— (80) 60	N.M.	134	.32	43	183	0.6	3.5	4.80
B.S. Preop.	1.81	203	5.3	3.8	2.1	95	40	5	26/— 2	20/— (14) 10	14	—	0.42	16	190/— 18	100/— (90) 70	110/— (96) 70	N.M.	180	.38	60	105	0.3	2.9	5.42
Postop.	1.80	198	4.4	4.5	2.5	97	47	3	25/— 4	20/— (10) 9	—	357	0.36	8	140/— 10	—	100/— (80) 60	N.M.	116	.26	31	179	0.7	2.9	4.15

*Measured by planimetric integration.
**Not measurable.
***Damped.

The mean pulmonary artery pressure was either normal or slightly elevated in the majority of patients. Severe pulmonary hypertension was observed in one patient, J.H., who was in congestive heart failure on admission to the hospital.

The pulmonary "capillary" pressure was within normal limits in seven patients, elevated in two, and not obtained in two.

The left atrial pressure was similar in magnitude and contour to the pulmonary capillary pressure (Fig. 4). The left atrial pressure curve exhibited prominent "a" waves in those patients with normal sinus rhythm.

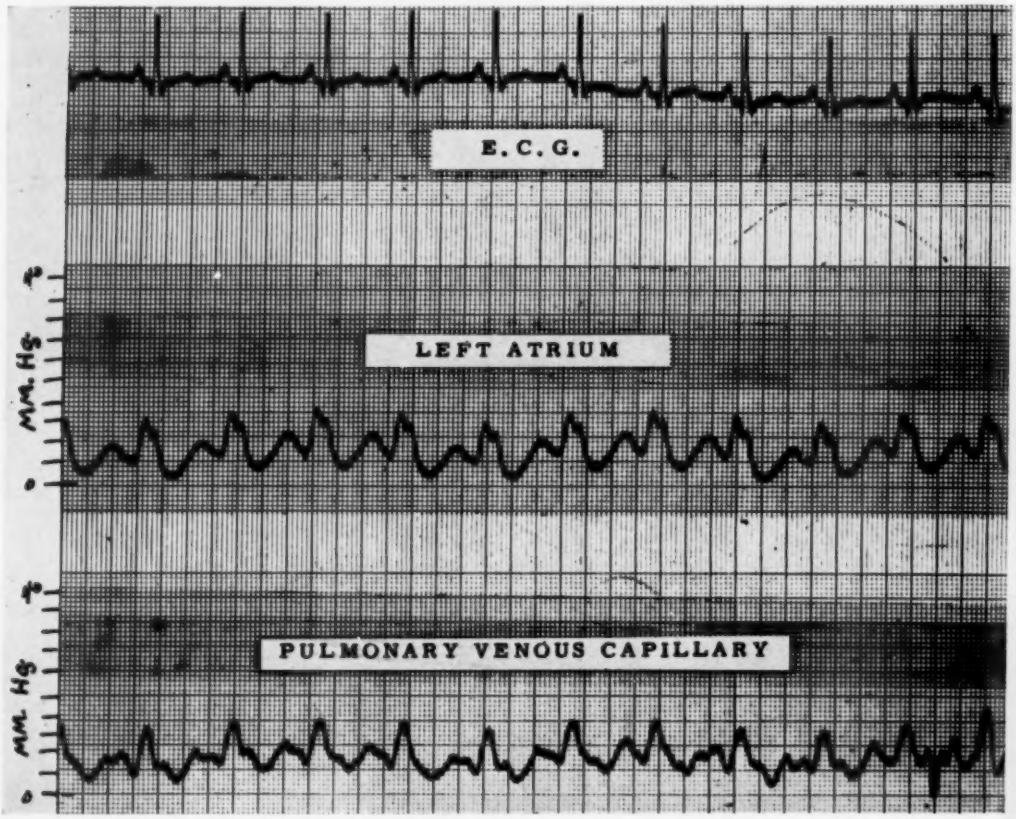


Fig. 4.—Pulmonary "capillary" (below) and left atrial (middle) pressure tracings recorded simultaneously with the ECG above.

The end-diastolic pressure in the left ventricle was elevated, greater than 10 mm. Hg, in all cases except one (S.F.), ranging between 7 and 28 mm. Hg. The systolic pressure in the left ventricle was 150 mm. Hg or above in all patients except one, ranging between 150 and 232 mm. Hg. The latter patient, J.S., had atrial fibrillation and his left ventricular systolic pressure varied between 104 and 160 mm. Hg.

The brachial artery pressure varied between 96 and 142 mm. Hg (systolic pressure) and between 70 and 100 diastolic except in the patient with atrial fibrillation. The pulse pressures varied between 30 and 60 mm. Hg, being within normal limits generally. The brachial artery pressure tracings were

similar to those cases reported previously.[3] An anacrotic notch or slur was observed on the upstroke with a delay to the peak of systole, ranging between 0.14 and 0.24 sec. (average: 0.2 sec.) in nine cases (normal: 0.08 to 0.12 sec.). The dicrotic limb appeared normal.

There was no constant relationship between the stroke volume, pressure gradient, aortic valve area, and the position of the anacrotic notch on the upstroke.

A constant finding in aortic stenosis was the presence of a systolic pressure gradient between the left ventricle and aorta or brachial artery (Fig. 2). The aorta was entered in seven patients. The aortic and brachial artery pressures were similar in magnitude in three. In the other four, the systolic pressure in the brachial artery exceeded the central aortic pressure by 10 to 20 mm. Hg. The left ventricular-brachial artery pressure gradient measured by planimetry varied between 25 and 74 mm. Hg. This value obtained directly from the pressure tracings ranged between 30 to 110 mm. Hg except in the patient with atrial fibrillation. In the latter case, the pressure gradient varied from beat to beat (8 to 36 mm. Hg).

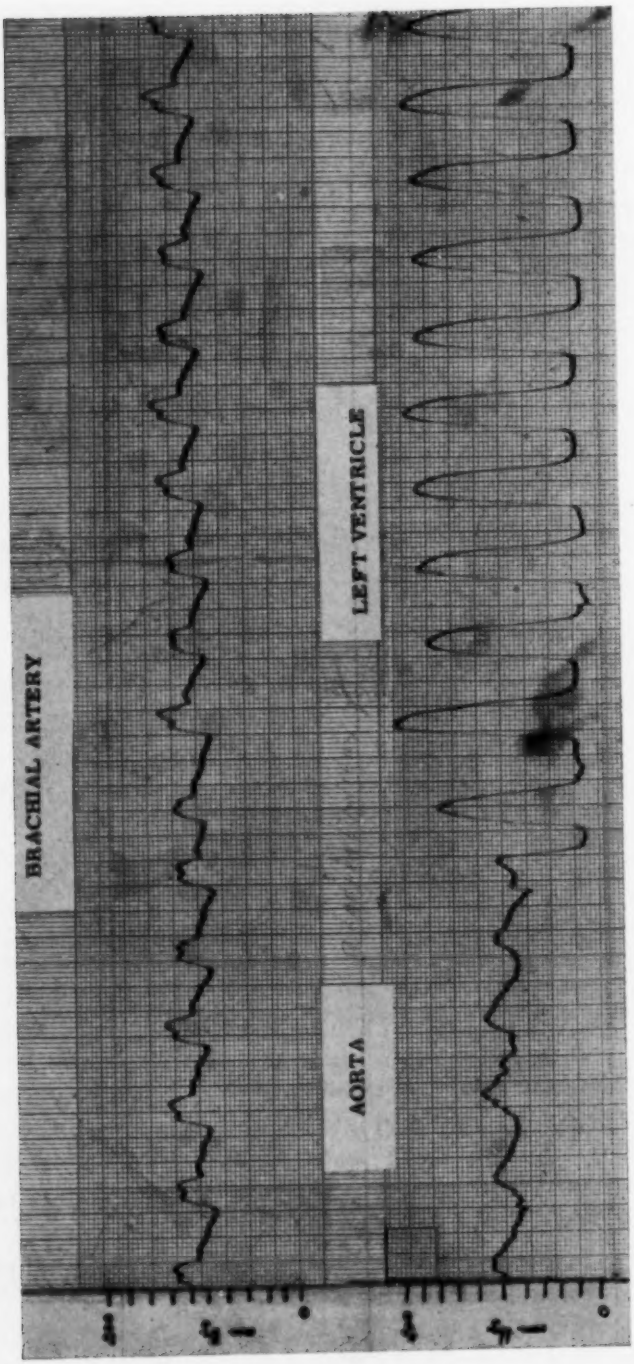
The aortic valve flow, generally reduced below normal, varied between 81 and 243 c.c./S.E.P. sec., averaging 140 c.c./S.E.P. sec. The calculated aortic valve areas were markedly reduced and were below 1 cm.^{2} in all cases ranging between 0.2 and 0.9 cm.^{2} (average: 0.5 cm.^{2}).

The work of the right ventricle was within normal limits or low in all cases. The total work of the left ventricle was elevated generally and ranged between 1.80 and 6.65 Kg.M./min. (average: 4.76 Kg.M./min.). It was below normal in patient J.S., despite severe obstruction, because of a markedly reduced cardiac output. The effective work of the left ventricle was generally lower and ranged between 1.12 and 3.86 Kg.M./min. (average: 2.88 Kg.M./min.).

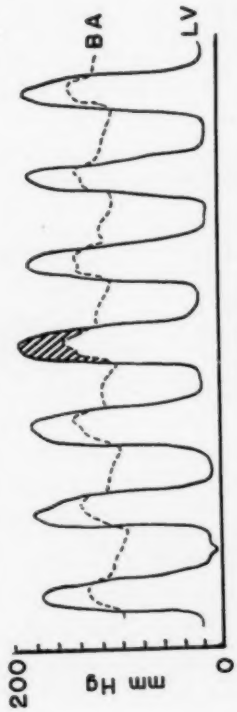
Aortic Stenosis—Postoperative Studies.—Three patients were studied again fourteen days following aortic commissurotomy. The pre- and postoperative data are shown in Table III,*B*.

In the first case, M.M., the systolic pressure gradient across the aortic valve was eliminated by surgery (Fig. 5). The mean systolic ejection pressure of the left ventricle fell from 190 to 102 mm. Hg, while the end-diastolic pressure was essentially unchanged, remaining elevated. The brachial artery and aortic pressures were also reduced. The cardiac output and aortic valve flows changed little. The aortic valve area preoperatively was 0.5 cm.^{2} In the absence of a pressure gradient postoperatively, the area could not be estimated. The systolic ejection period was decreased and the total work of the left ventricle was reduced markedly, from 4.9 to 2.7 Kg.M./min.

In the second case, C. McD., the systolic pressure in the left ventricle and brachial artery fell almost proportionately so that there was little change in the systolic pressure gradient (55 to 43 mm. Hg). The cardiac output and aortic valve flow increased slightly. There was little change in the aortic valve area. There was no change in the systolic ejection period or work of the left ventricle following surgery. The end-diastolic pressure in the left ventricle fell from 26 to 20 mm. Hg. This patient had a heavily calcified aortic valve.



5, *A*.



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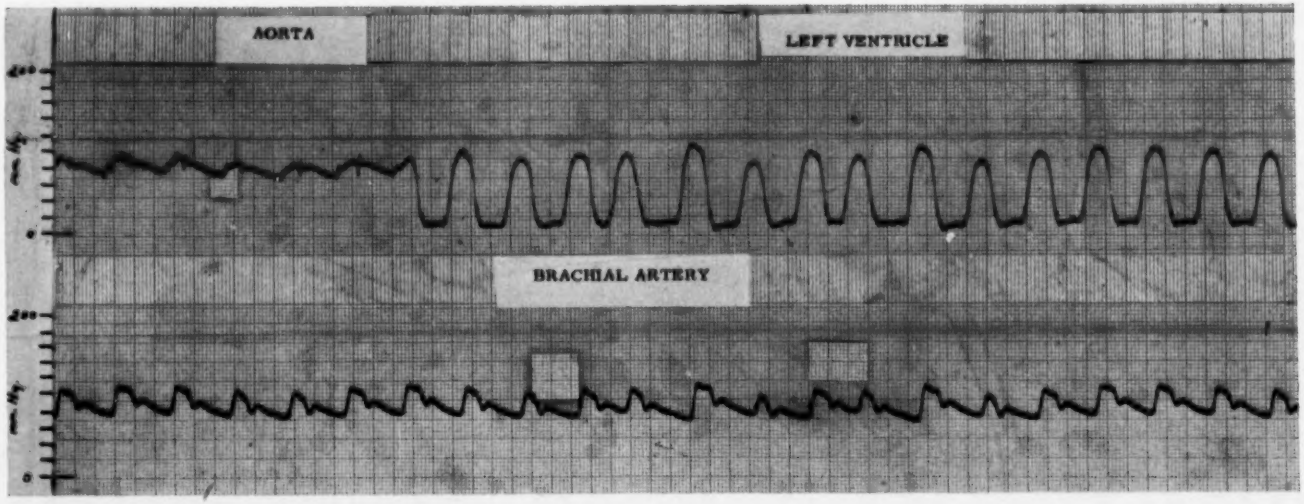
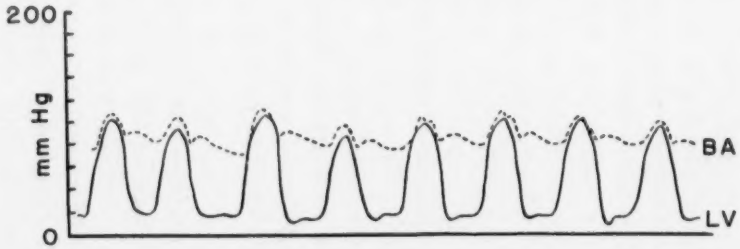


5, *C*.



5, *D*.

Fig. 5.—Aortic stenosis (Patient M.M.): *A*, Preoperatively. Continuous pressure recording from aorta to left ventricle (lower) and brachial artery (above). *B*, Same as *A*. Left ventricular and brachial artery pressures redrawn and superimposed. Note pressure gradient. Aortic valve area —0.5 cm.². *C*, Same patient, postaortic commissurotomy. Note elimination of gradient between aorta and left ventricle. *D*, Same as *B*. Note negative pressure gradient between left ventricle and brachial artery. Aortic valve area not calculable in absence of gradient.

In the third case, B.S., the cardiac output and aortic valve flow increased following surgery. The systolic and diastolic pressures in the left ventricle decreased. The pressure in the brachial artery fell slightly. The systolic pressure gradient decreased despite the increase in flow. The aortic valve area thus increased.

DISCUSSION

Simultaneous catheterization of the left and right heart makes it possible to assess the dynamics of the circulation more completely than previously. Pressures may be recorded from all cardiac chambers and great vessels. The cardiac output and flows across the valves may be determined by the direct Fick method at the same time.

In the present study, this combined procedure was applied to evaluate the altered hemodynamics in patients with mitral stenosis and aortic stenosis. Simultaneous estimation of the pressure-flow relationships across the obstructed valves allowed for estimation of the orifice size.

In the three individuals with normal cardiovascular systems studied, the pressures within the right heart chambers and pulmonary circuit were within normal limits. The human left atrial pressure tracing is similar to that shown by Wiggers[10] in experimental animals.

From the data obtained it would appear that the end-diastolic pressure of a normal left ventricle is somewhat higher than that of a normal right ventricle. Factors influencing this value include the relative thickness of the two chambers and the diastolic blood volume.

Absence of measurable pressure gradients across normal mitral and aortic valves precludes the calculation of valve areas by the hydraulic formulae. These values are considered to be 4 to 6 cm.^{2} for the mitral and 3 cm.^{2} for the aortic valve.

Mitral Stenosis.—The findings by right heart catheterization in the patients with mitral stenosis in this series agree with those previously reported.[1,2] The cardiac output generally was low. The extraction of oxygen by the tissues as shown by the arteriovenous oxygen difference was increased. The mean pulmonary artery and "capillary" pressures were generally elevated.

The constant finding revealed by the left heart catheterization was the presence of a pressure gradient during ventricular filling (V.F.G.). It has been pointed out that this is more accurately referred to as the "ventricular filling pressure gradient" rather than *diastolic* gradient since this period includes a small portion of early ventricular systole (Fig. 1).[11]

The calculated mitral valve areas in this group correspond with those reported by Lewis and associates.[12] The validity of application of the formula to patients with mitral stenosis has been discussed by several authors.[9,13] It was pointed out that this formula applies to a fixed orifice which is more likely in mitral stenosis than in the normal. The formula made no correction for intermittent flow. Since a pressure gradient is observed throughout "diastole" in mitral stenosis, flow across the mitral valve occurs more evenly during ventricular filling, in marked contrast to a normal mitral valve. The influence of

shape of the valve is considered to be small.[13] It has been pointed out that this formula is more applicable to stenotic orifices with turbulent flow than Poisseuille's Law as recommended by Silber and associates.[14]

In the formula originally proposed by Gorlin and Gorlin, the pressure gradient was determined from the pulmonary venous capillary pressure. In this study the actual pressure gradient between the left atrium and left ventricle, during filling of the latter, was measured planimetrically from the respective pressure tracings. At smaller areas the modified formula gave slightly higher values than the original formula, while at higher areas the reverse was true (Table IV). A possible source of disagreement between the original and modified formulae may be found in the use of 0.7 for the C-factor. It is possible that the constant need be greater than reported originally. Both the original and modified formulae gave areas which were greater than those estimated by the surgeon. Since the orifice is often slitlike, it is difficult for the surgeon to estimate the entire valve area digitally. The calculated area, therefore, probably represents the "functional valve area" rather than the anatomic size estimated by the surgeon.

TABLE IV. COMPARISON OF MITRAL VALVE AREAS BY THE ORIGINAL AND MODIFIED GORLIN FORMULA WITH SURGEON'S ESTIMATE

PATIENT	MODIFIED GORLIN (CM.^{2})	ORIGINAL GORLIN (CM.^{2})	SURGEON'S ESTIMATE
A.V.	0.7	0.3	0.4
L.S.	0.5	0.4	*
H.D.	0.7	**	0.9
M.F.	0.7	0.6	0.4
M.S.	0.9	0.6	0.4
D.M.	0.8	0.6	0.3
A.S.	1.1	0.9	<0.5
M.K.	1.1	0.6	0.9
R.R.	1.1	1.5	0.4
I.G.	1.3	1.4	0.9
H.M.	1.2	1.4	1.2

*Patient had cardiac arrest at time of surgery. Emergency mitral commissurotomy was performed.
**Pulmonary venous "capillary" pressure not obtained.

In the presence of mitral regurgitation, the calculated area will be smaller than the actual valve size, since the estimated mitral valve flow by the direct Fick method does not include the regurgitant flow. Hence, only patients with pure mitral stenosis were included in this study.

The ventricular filling gradient varied widely with similar valve orifice sizes. The flow similarly varied widely, although there was a tendency for the smaller flows to exist in patients with smaller areas. As expected, for a given valve area, the larger flows were accompanied by larger pressure gradients. For example, in patients H.D. and M.F., with mitral valve areas of 0.7 cm.^{2} each, mitral valve flows of 68 and 104 c.c./V.F.P. sec. were accompanied by pressure gradients of 9 and 25 mm. Hg, respectively. This was also true for patients C.M. and D.M. (Table II,*A*).

Similarly, the mean left atrial pressures, which were constantly elevated, varied widely throughout the range of valve areas observed. The higher pressures were associated with the larger flows in patients with similar valve areas (patients A.V. and M.F.; I.G. and H.M.). The left atrial pressure tracings demonstrated giant "a" waves in patients with normal sinus rhythm, representing forceful atrial contractions. With obstruction to flow across the stenotic mitral valve, rapid filling of the ventricle does not occur. The "v" wave is thus less prominent. The rise in atrial pressure during diastasis, the slow filling period of the ventricle, is absent in mitral stenosis since the pressure in the atrium is constantly higher than that in the ventricle during this time.[11]

In atrial fibrillation, the left atrial pressure tracing consisted of a "c-v" wave with an attenuated x wave. We have observed this type of contour in the absence of mitral regurgitation.[8] Ankeney and associates[15] have pointed out that the x wave is related to relaxation following atrial contraction. In the absence of the latter in atrial fibrillation, the x wave may thus be absent or markedly attenuated.

In this study, there was generally good agreement between simultaneously recorded pulmonary venous "capillary" and left atrial pressures both in contour and magnitude. This is in agreement with observations made by others under different circumstances.[16]

The pulmonary artery pressure varied widely for similar valve areas in the group studied. Pulmonary hypertension to the same degree was observed at all degrees of obstruction. For example, in patients H.P., C.M., and I.G., with valve areas of 0.6, 0.8, and 1.3 $cm.^2$, respectively, the mean pulmonary artery pressures were 40, 40, and 41 mm. Hg. The height of the pulmonary artery pressures, therefore, did not necessarily reflect the degree of mitral obstruction. In patients I.G. and H.M. with valve areas of 1.3 and 1.2 $cm.^2$, the mean pulmonary artery pressures were 41 and 18 mm. Hg, respectively. In these patients, the pulmonary vascular resistances were similar and the higher pressure was associated with a greater flow.

The increase in pulmonary artery pressure did not always correspond proportionately to the increase in mitral valve flow. This is to be expected since the pressure in the pulmonary circuit not always reflects back pressure from the obstructed mitral valve, but is also an expression of the increased vascular resistance secondary to vascular changes.

When the degree of obstruction and flow across the mitral valve were similar, differences in height of pulmonary artery pressure reflected differences in pulmonary vascular resistance. This is demonstrated in a comparison of patients A.V. and H.D. The mitral valve areas in these individuals were 0.7 $cm.^2$ each and flows were 70 and 68 c.c./V.F.P. sec. The mean pulmonary artery pressures were 24 and 40 mm. Hg, while the pulmonary vascular resistances were 178 and 661 dynes $sec./cm.^{-5}$, respectively.

The pulmonary vascular resistance was not determined necessarily by the degree of mitral obstruction. Although the lower resistances were observed in patients with larger valve areas, the pulmonary vascular resistance may be widely different with similar valve areas (e.g., in patients A.V. and M.F., A.S. and H.M.).

Similarly, right ventricular work varied with similar degrees of mitral obstruction. This is not surprising since right ventricular work is determined by the cardiac output and the mean pulmonary artery pressure. Since both of these factors may vary widely at similar valve areas, the right ventricular work varied accordingly.

In summary, evaluation of the degree of obstruction at the mitral valve requires a knowledge of the pressure-flow relationships. Pressure gradients alone do not provide sufficient information, since they are in turn dependent upon the existing rates of flow. Although the latter are affected to a degree by the size of the mitral valve, they vary considerably for similar valve areas. Furthermore, the pressures within the pulmonary circuit do not always reflect the degree of mitral obstruction. When the pulmonary vascular resistance and degree of mitral obstruction are constant, the rate of flow varies with the height of the pulmonary artery pressure. When the degree of mitral obstruction and rate of flow across the valve are constant, the height of the pulmonary artery pressure is a reflection of the pulmonary vascular resistance.

Aortic Stenosis.—A constant finding in patients with aortic stenosis is the presence of a pressure gradient between the left ventricle and aorta or brachial artery during ventricular systole. There is no measurable gradient across a normal aortic valve, whether it be in a normal individual or in a patient with pure mitral stenosis. A negative gradient exists normally between the left ventricle and brachial artery as well as between the central aorta and brachial artery. This has been attributed to reflected waves from the periphery.[10] This concept has been opened to question recently.[17]

Although the central and peripheral pressures may be similar in aortic stenosis, this is not invariably the case as shown by our data. This is at variance with that reported by Wright and associates.[18]

The aortic valve area averaged 0.5 cm.^{2} for the group studied. This area is considered critical for the aortic valve, below which clinical symptoms appear.[19] The validity of applicability of the formula to aortic stenosis was ascertained in one patient in this group. This patient, J.S., died at the time of surgery, prior to cardiotomy. The intact heart was perfused on a McMillin-type cyclic perfusion apparatus[20] and a picture of the valve taken during the height of systole. Planimetric measurement of the actual valve size was 0.4 cm.^{2} while the area calculated from the hemodynamic data prior to death was 0.5 cm.^{2}.

The present studies indicate that the pressure gradient is not dependent upon the aortic valve area alone, similar gradients occurring at different areas. However, for a given valve area, as expected, the pressure gradient varied as the rate of flow. In patients J.S. and S. Be. with aortic valve areas of 0.5 cm.,^{2} the pressure gradients were 28 and 57 mm. Hg with flows of 116 and 193 c.c./S.E.P. sec., respectively.

Although the aortic valve flow varied widely, there was a tendency for the smaller valve orifices to be accompanied by the smaller flows. The cardiac output for the group as a whole was below normal. As reported previously[3] the limited cardiac output may be attributed to (a) left ventricular failure and (b) the obstruction per se at the aortic valve. There were five patients,

J.S., C.McD., S.Be., J.B., and J.H., who were in congestive heart failure at the time of admission to the hospital. These cases were vigorously treated with bed rest, digitalis, low salt diet, and mercurial diuretics and considered clinically out of failure at the time of the present study. The other patients had no signs of failure. Although the cardiac outputs were lower in the group with failure on admission, they were below normal in the remaining patients as well. Hence, the obstruction at the aortic valve per se may be a limiting factor in maintaining an adequate systemic blood flow.

In aortic stenosis, the left ventricle compensates for the obstruction by hypertrophy. This hypertrophied muscle is able to perform more work. Unfortunately, the coronary artery system cannot increase pari passu with increase in muscle mass.[21] Thus the coronary flow is unable to increase to meet the demands of the left ventricle. The prolongation of systole and increased systolic resistance may further limit coronary perfusion.[22] Under such circumstances, the left ventricle may not be able to increase the intraventricular pressure sufficiently to maintain a normal blood flow.

When the cardiac output is unable to meet the demands of the tissues, the extraction of oxygen by the latter is increased. This is demonstrated in the widening of the arteriovenous oxygen difference, which is particularly marked during exercise.[3]

Left ventricular function is greatly altered by aortic stenosis. The systolic ejection period is prolonged. The systolic pressure in the left ventricle may be one and one-half to twice that in the normal or in patients with mitral stenosis. The end-diastolic pressure in the left ventricle is greatly elevated. This finding did not correlate with the presence of left ventricular failure clinically. Although the end-diastolic pressure was elevated in the patients who were in failure at the time of admission to the hospital, it was similarly elevated in those with minimal symptoms. It would appear that elevation of the end-diastolic pressure in the left ventricle in these patients results from the altered pressure-volume elasticity relationships characteristic of hypertrophy. This is suggested from the data obtained in patient M.M. before and after aortic commissurotomy. At the time of the study, fourteen days following surgery, there was elimination of the pre-existing pressure gradient across the aortic valve. The left ventricular systolic pressure and total left ventricular work fell appreciably. However, the end-diastolic pressure in the left ventricle changed little. This is attributable to the persistence of hypertrophy of this chamber. There was no evidence of left ventricular failure at any time in this patient.

Similarly, the left atrial pressure may be elevated due to (a) left ventricular failure or (b) altered pressure-volume relationships of the left atrium. The decreased distensibility of the left ventricle offers increased resistance to filling of this chamber. As a result the left atrium hypertrophies. These circumstances give rise to the giant "a" waves observed in the left atrial pressure tracing. Since the "a" wave occurs late in ventricular diastole, the mean left atrial pressure in these patients was frequently lower than the end-diastolic pressure of the left ventricle. Thus the mean left atrial pressure did not always reflect the filling pressure of the ventricle.

The abnormalities in the brachial artery pressure tracings in our present study were similar to those reported previously by us.[3] The degree of stenosis could not be estimated from the contour of the peripheral pulse. There was no correlation between the stroke volume, pressure gradient, or degree of stenosis, and the position of the anacrotic notch or time to peak of systole in the brachial artery pressure tracing.[23]

The pulmonary artery pressures are generally within normal limits or slightly elevated in aortic stenosis. Severe pulmonary hypertension is most frequently observed when the lesion is accompanied by failure, but could result from pulmonary vascular changes.[3]

Combined heart catheterization allows for estimation of the total work of the left ventricle in aortic stenosis, which was not possible previously. The total left ventricular work in this lesion is generally increased and may be as great as twice normal. Occasionally, the work is within normal limits or below (patients J.S. and J.H.), despite severe obstruction, whenever the cardiac output is markedly reduced.

In summary, aortic stenosis is constantly accompanied by a pressure gradient across the aortic valve. This gradient helps to maintain the systemic blood flow. The latter becomes generally reduced with increasing degrees of obstruction. Estimation of the degree of aortic obstruction cannot be made by pressure gradient alone, but requires knowledge of the flow as well. Aortic stenosis leads to increased work of the left ventricle, resulting in hypertrophy of this chamber. Hypertrophy, in turn, alters the pressure-volume elasticity relationships of the chamber, resulting in elevation of its end-diastolic pressure. The latter may occur before left ventricular failure appears clinically. This increased resistance to filling of the left ventricle reflects itself in hypertrophy of the left atrium with production of giant "a" waves. Pulmonary hypertension results from left ventricular failure or pulmonary vascular changes. This, in turn, places a strain upon the right ventricle.

EVALUATION OF VALVULAR SURGERY

In addition to assessing the altered dynamics of valvular lesions, combined heart catheterization may be employed in the evaluation of surgical techniques for their correction. Right heart catheterization has not proved entirely satisfactory in evaluating mitral commissurotomy. Changes in cardiac output are inconstantly observed. Pulmonary artery pressures do not always fall. This may be expected since pulmonary hypertension does not always reflect *only* back pressure from the stenotic mitral valve, but may represent an expression of increased pulmonary vascular resistance. Right heart catheterization is of even less value in defining the dynamics at the aortic valve. Hence, it is of little use in evaluating aortic valve surgery.

Since the sine qua non of obstruction is the presence of a pressure gradient across the valve, it would seem that comparison of this measurement pre- and postoperatively should be of aid in assessing the dynamic effects of surgery. However, as shown by the present study, the significance of the changes in the pressure gradients requires a knowledge of the existing flows. Hence, simul-

taneous estimation of the pressure gradient and cardiac output before and after surgery should prove invaluable in not only determining the changes in the circulatory dynamics following surgery, but in evaluation of the surgical techniques. Finally, it is hoped that further studies along these lines on larger series of cases will provide better criteria for the selection of patients for valvular surgery.

SUMMARY

1. Simultaneous catheterization of the left and right heart was performed thirty-three times in twenty-six individuals; three with normal cardiovascular systems; twelve with mitral stenosis; and eleven with aortic stenosis.

2. Cardiac output and pressure gradients were obtained simultaneously and the orifice size calculated.

3. The constant physiologic abnormality in mitral stenosis was the presence of a ventricular filling pressure gradient. The latter alone did not reflect the degree of mitral obstruction. The gradient was influenced by the rate of blood flow across the mitral valve.

The height of the pulmonary artery pressure was not necessarily a measure of the degree of stenosis. When the degree of mitral obstruction and pulmonary vascular resistance were constant, the rate of blood flow varied with the height of the pulmonary artery pressure. When the degree of mitral obstruction and rate of blood flow across the valve were constant, the height of the pulmonary artery pressure reflected the degree of pulmonary vascular resistance.

4. Aortic stenosis was accompanied constantly by a pressure gradient across the aortic valve during ventricular systole. The systemic blood flow was generally reduced and was a function of the pressure gradient and degree of aortic obstruction. The gradient alone was not an accurate measure of the degree of obstruction.

In aortic stenosis, the pressure-volume elasticity relationships of the left ventricle are altered as a result of hypertrophy reflecting itself in elevation of the end-diastolic pressure. This did not correlate with clinical left ventricular failure. Total left ventricular work was one and one-half to two times normal. Giant "a" waves were characteristically observed in the left atrial pressure tracings.

5. Estimation of the degree of obstruction at the mitral and aortic valves requires a knowledge of the pressure-flow relationships.

6. The applicability of combined heart catheterization in evaluating patients for cardiac surgery and surgical techniques for correction of stenotic valvular lesions is demonstrated.

The authors wish to express their appreciation to the Misses Ruth Freeman, Betty Underwood, and Evelyn DiSimone, for their technical assistance, and to the other members of the catheterization team, also.

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THE TELECARDIOGRAM

W. EINTHOVEN

Translated by

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TWO lectures by W. Einthoven in May and November, 1905, were the source of an article on "The Telecardiogram" in the *Archives Internationales de Physiologie* 4:132, 1906. This fascinating work is the first organized presentation of normal and abnormal electrocardiograms recorded with the string galvanometer. These were made with galvanometer and recording apparatus in Einthoven's laboratory, the impulses transmitted through telephone wire from the patients in a hospital some distance away. Einthoven's explanations for the recorded phenomena are for the most part remarkably clear and accurate, if not complete. The following is a somewhat free translation of the bulk of the paper. An earlier translation of the first portion of this paper, on the technical aspects of "long distance" recording, appeared in the AMERICAN HEART JOURNAL **49:77**, 1955.

Modern terminology is used primarily to promote readability, but certain vernacular terms are left for their historical interest. Einthoven refers to waves as summits, had no term for complex, and had not yet numbered his lead derivations. For example, he writes of "current taken from right hand to left foot" rather than potential difference in Lead II.

Translation begins with paragraph 35.

35* Fig. 16 is a reproduction of the first long-distance electrocardiogram we recorded, that of a healthy and vigorous man, the current derived from the

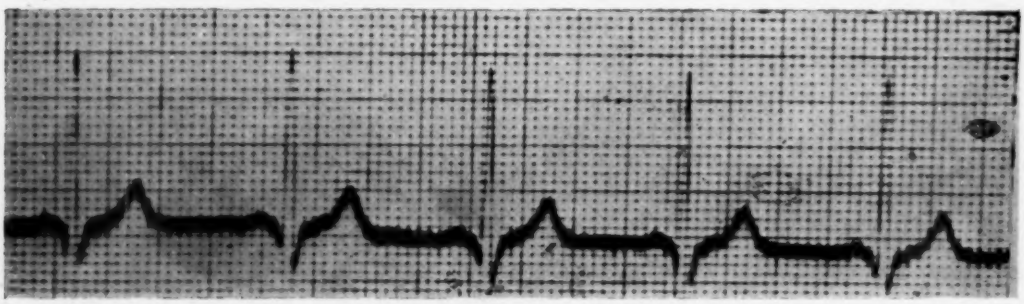

Fig. 16.—D. J. Derived from right hand to left hand.

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*The numbers of both paragraphs and figures are those of the original paper.

two hands.* It differs in no way from the record made with the subject in the laboratory beside the galvanometer. In each instance the five summits, P produced by auricular systole, Q,R,S, and T by ventricular systole, are identical in form and amplitude. In this subject the R wave is particularly high, corresponding to a potential difference of two millivolts.†

36. We will now examine cardiograms from patients hospitalized with divers cardiac diseases. In examining patients we are obviously motivated by the desire to cure their disease. Such, indeed, is the ultimate goal of the physician. Unfortunately, we must be quite modest since cure is not so readily obtainable. We must initially seek to understand cardiac function in detail and the causes of its numerous disturbances. With clearer outlook based on this knowledge we may be able in the remote future to relieve suffering and restore health to patients.

37. Fig. 17 presents the left hand-left foot electrocardiogram of a patient with mitral valve disease, predominantly insufficiency.

One notes specially the upwardly directed complex of colossal amplitude. It reaches almost 30 mm., which corresponds to a potential difference of 3 millivolts.

38. I have no comparable electrocardiogram obtained from the left hand-left foot. We would be in error, nevertheless, to consider this form as characteristic of mitral disease. Our diagnosis of valvular defect should not rest exclusively on the electrocardiogram since it does not record actual valve motion. The tracing is rather a manifestation of cardiac muscle contraction and is modified only to the degree that defective valve action influences this contraction.

39. The way in which the heart contracts depends largely upon the extent of disease in the muscle itself and the degree of compensation extant. In this particular case we must compare the degree of insufficiency with the magnitude of the other mitral defects. Only extensive study will reveal the full significance of the electrocardiogram.

40. In comparison, Figs. 18 and 19 are telecardiograms on patients with aortic insufficiency. The recording is from left hand-left foot and the waves are the reverse of those in the case of mitral insufficiency, the principal ventricular deflection being downward.

41. Mitral insufficiency provokes a predominant right ventricular hypertrophy, and aortic insufficiency a left ventricular hypertrophy. It is natural to presume that right hypertrophy is accompanied by development of an upright R and left hypertrophy by a downard R in electrocardiograms obtained from left hand-left foot.

42. This supposition is confirmed in Fig. 20 from a patient with arteriosclerosis and marked left heart hypertrophy. The R wave is directed downward with an amplitude corresponding to 2 millivolts potential difference.

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*This telecardiogram was recorded March 22, 1905. As a result of careful preparation the first attempt was an immediate success. To date, February 24, 1906, we have recorded a hundred cardiograms and several murmurs from hospitalized patients with no interruption of our operation. The galvanometer and recording apparatus and the communicating wires to the hospital have remained in perfect condition.

†The considerable R amplitude in this case was partly occasioned by the patient's physical exertion just before the experiment. He had gone by bicycle from our laboratory to the hospital.

Fig. 17.

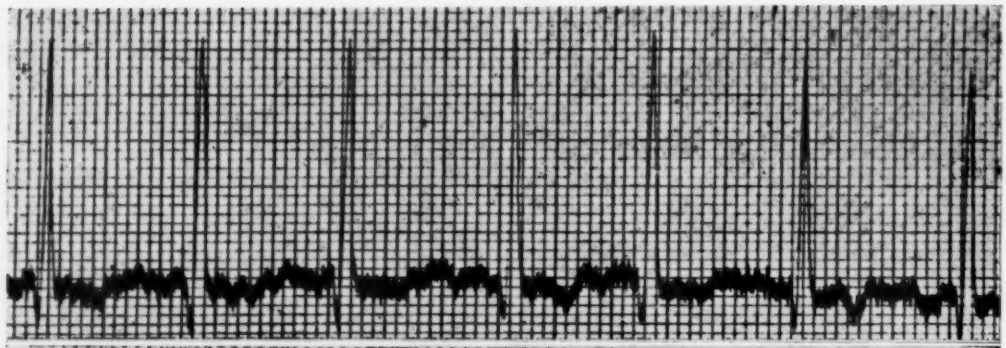

Fig. 18.

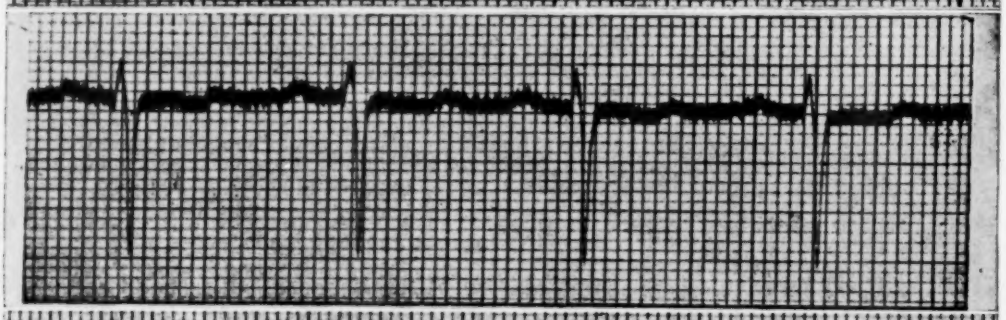

Fig. 19.

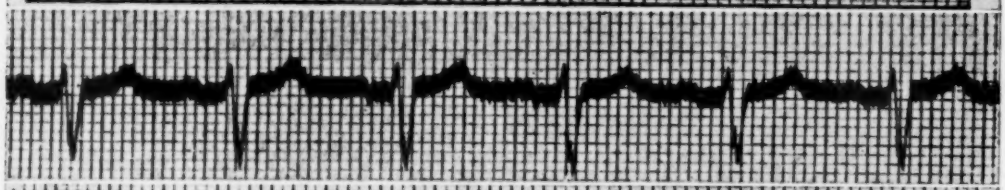

Fig. 20.

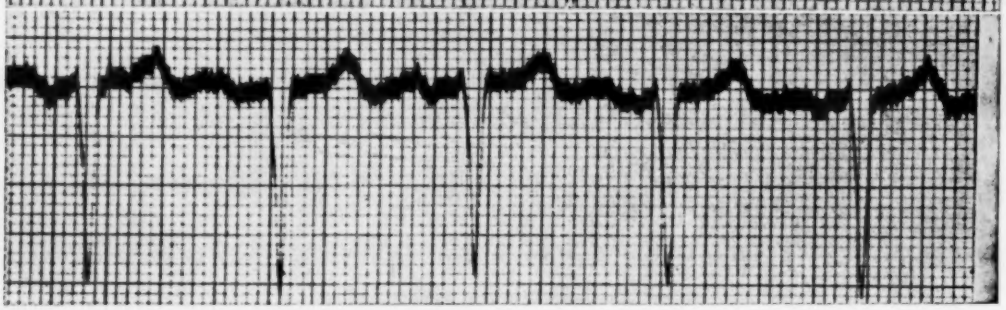

Fig. 17.—A. B. Mitral insufficiency—left hand to left foot.

Fig. 18.—B. H. S. Aortic insufficiency—left hand to left foot.

Fig. 19.—C. d. G. Aortic insufficiency—left hand to left foot.

Fig. 20.—J. V. J. Left ventricular hypertrophy—left hand to left foot.

43. Fig. 21 reproduces the telecardiogram of a patient with mitral stenosis without insufficiency and is taken from left hand-left foot. Note especially the characteristic form of the P wave, clearly accentuated and separated into three or four components.

44. This augmentation and prolongation of auricular systole is evidently related directly to the existence of mitral stenosis. The stenotic obstruction to blood flow causes a compensatory effect on the part of auricular contraction. To

my knowledge no one has previously been able to demonstrate this change in the left auricle, which is the most important of the two. The method of venous pulse recording, so valuable in study of the right auricle, has no application to study of the pulmonary veins in man, due to insurmountable anatomic obstacles.

45. In a second case of mitral stenosis, recorded from right hand-left foot in Fig. 22, the P wave is less prolonged but enormously elevated in comparison to the normal P in Figs. 7 and 8.

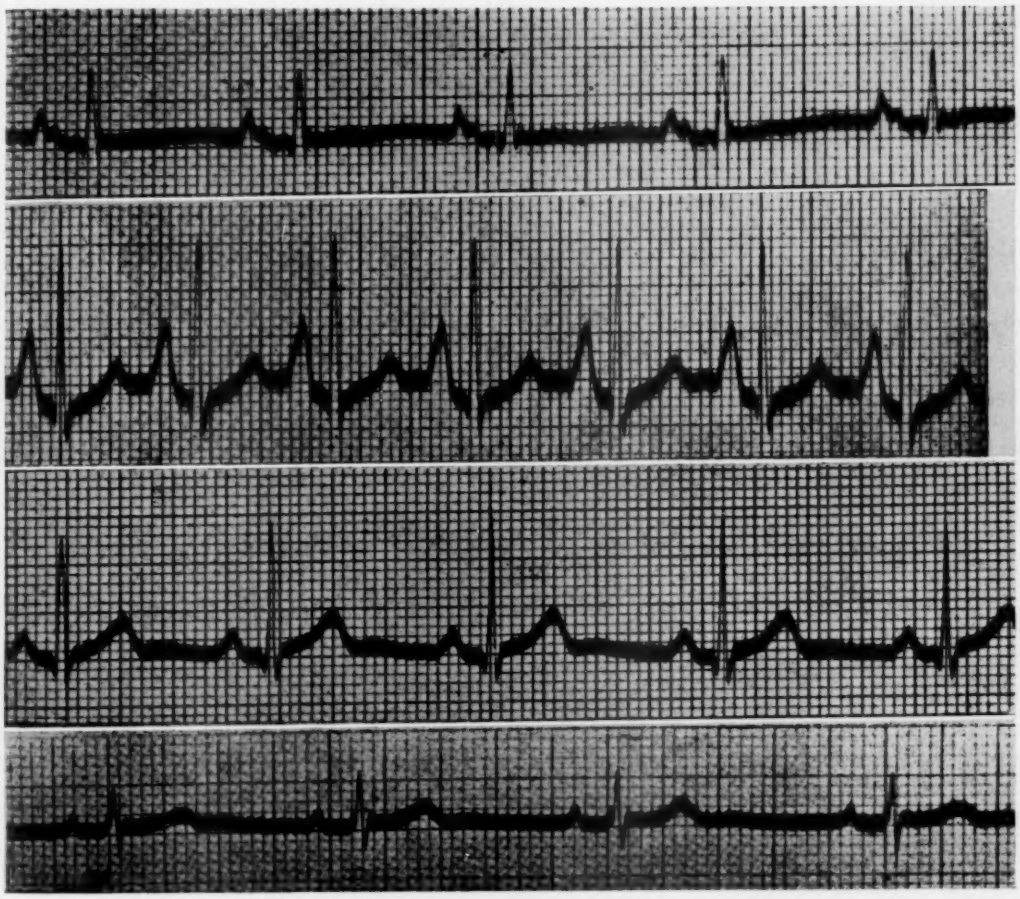

Fig. 21.

Fig. 22.

Fig. 7.

Fig. 8.

Fig. 21.—V. d. A. Mitral stenosis—left hand to left foot.
Fig. 22.—G. d. R. Mitral stenosis—right hand to left foot.
Fig. 7.—M. Right hand to left foot.
Fig. 8.—M. Left hand to left foot.

46. I have reproduced in Fig. 23 a most remarkable electrocardiogram from a patient with degenerative heart disease. The current is derived from right hand-left foot. We observe here that following the T wave, the last deflection in all our other electrocardiograms, there appears another wave. This peak, which we call U, terminates about 0.5 sec. after the onset of systole. This demonstrates in this pathologic case that systole lasts at least 0.5 sec. and is characterized by both an irregular and prolonged contraction.

47. Fig. 24, a left hand-left foot tracing from a case of congenital heart disease, is difficult to analyze in all its detail. In the upward directed complex we observe a notching not seen in a normal electrocardiogram.

48. We see remarkable changes in the waves in instances of functional disturbance from intemperate sport activity. And again, a great number of other abnormal situations, too numerous to mention here, exercise their influence on the electrocardiogram.

Fig. 23.

Fig. 24.

Fig. 25.

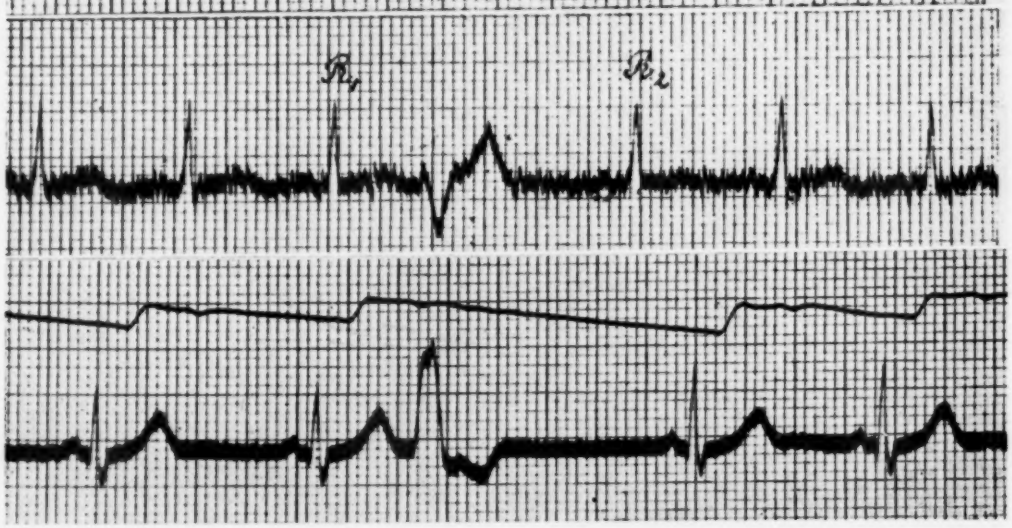

Fig. 26.

Fig. 23.—A. V. Y. Degenerative heart disease—right hand to left foot.
Fig. 24.—Ch. N. Congenital heart disease—left hand to left foot.
Fig. 25.—D. H. Convalescence in typhoid fever—right hand to left hand.
Fig. 26.—R. Dropped beat—right hand to left hand.

49. Anomalies in heart position can modify the form of the electrocardiogram in the presence of normal cardiac function. Since it is precisely the manner in which the heart functions that we are trying to deduce with an electrocardiogram, we must pass judgment independent of the effect of heart position on the tracing. This is why we must examine recordings on each subject derived from different vantages. Practically, we have always applied the three derivations right hand-left hand, right hand-left foot, and left hand-left foot.

50. I would now like to draw attention to a phenomenon observed in the course of our work which has occasioned considerable surprise.

51. It is a well-known fact that in a person with a regular pulse the rhythm may suddenly be interrupted. From time to time a beat is dropped in a regular series of beats. This irregularity is especially found in persons who have suffered debilitating illness, such as typhoid fever. One would expect to see at the moment of the dropped pulse beat an electrocardiographic complex greatly diminished in amplitude or completely absent. It is therefore quite remarkable that at the moment of the dropped pulse beat there develops a relatively strong potential, often more intense than that of the normal ventricular complex.

52. Fig. 25 is a reproduction of the electrocardiogram in a patient convalescing from typhoid fever. The tracing is a bit tremulous but can otherwise be regarded as normal. Actually this tremor does not originate in potentials from cardiac contraction but from those of skeletal muscle, as I will demonstrate at another occasion. Between beats R_1 and R_2 an atypical complex appears. This atypical beat is the sole abnormality in a series of normal beats.

53. Fig. 26 is the simultaneous record of pulse and electrocardiogram made in our laboratory on a patient who had typhoid fever two years previously. We find that the pulse wave is absent shortly after the electrocardiographic manifestation of an atypical beat.

54. It is of note that the latter occurs a little before we would expect the normal beat in the electrocardiogram. There is reason, therefore, to consider the process accompanying the atypical complex as the cause of the dropped pulse. This abnormality of cardiac function consists of an extrasystole followed by a compensatory pause.

55. With this convalescent patient we made a striking observation. While we in the laboratory observed the galvanometer deflections the clinician in the hospital, Prof. Nolen, took the subject's pulse. Each time we observed an atypical deflection we warned the clinician of it by a short telephonic signal. He found after each warning signal a dropped beat in the pulse.

56. With careful palpation one can only detect a dropped beat toward the end of the instant a normal beat is awaited. Since the atypical galvanometer deflection appears before the expected beat it allows us to predict the absent pulse. Thus were we able, to the great surprise of Prof. Nolen, to warn him telephonically an instant before he was to observe a dropped beat.

58. It should be explained that this pulse wave was obtained from a tambour over the carotid. Though it seems unlikely, it is not impossible that altered blood flow in the jugular vein could have influenced the arterial curve.

59. Our observations at this time are insufficient to satisfactorily explain this negative pulse wave, but the phenomenon is so obvious I have thought it well not to pass over it. The depression at n in Fig. 27 is not an artifact since it is seen only at this point in a long series of beats and it occurs in another series at almost the same interval after an extrasystole. In Fig. 29 it is seen at n, 0.28 sec. after the atypical beat, and in Fig. 27, 0.32 sec. following. These intervals appear rather great to me and seem to establish that an atypical contraction exerts a relatively prolonged influence.

60. As seen in Fig. 28, it sometimes happens that an atypical beat occurs late. One then observes the interesting fact that the pulse is hardly disturbed.

61. It has long been known that cardiac contractions occur without producing a peripheral pulse. They have been described as extrasystoles, or inopportune beats, and their origin distinguished in auricles, bundle of His, or ventricles. They have been spoken of also as frustrated beats since the contraction is inadequate to overcome aortic pressure.

62. However, in these explanations we have failed to recognize the essence of the phenomenon. For example in Fig. 28 we cannot speak of an extrasystole, or of a frustrated beat, since the beat occurs in time and the pulse produced is quite evident.

63. The cause of the phenomenon must be sought in the manner in which the heart contracts. In describing extrasystoles we have probably been deceived by the findings on auscultation and by the strength of the pulse. We have thought that extra beats would inevitably be weaker the closer they followed the normal beat.

64. We find that, in reality, atypical beats occurring immediately after a normal beat differ little from those occurring after a normal, or nearly normal, pause. This is clearly seen in comparing Figs. 26 and 27 with Fig. 28. The time interval between normal and abnormal beats in Fig. 28 is on the order of six times greater than in Figs. 26 and 27 (end of T to beginning of QRS) while the amplitudes are not much larger.

65. Our viewpoint is confirmed by Fig. 29 in a right hand-left foot record from the same subject. The first extrasystole comes after a rather long pause and produces a prominent pulse wave *p*, while the second succeeds the normal beat almost immediately, producing only a small negative pulse wave at *n*.

66. There is an insignificant difference in the electrical appearance of the two abnormal beats.

67. I hardly need to say our conclusion is that the heart is already able to contract strongly soon after the end of the refractory period. This phenomenon is entirely in contradiction to some prevalent ideas about cardiac function.

68. It is more than probable that our atypical beats explain the phenomena called bigeminy of the heart, hemisystole, and alternans, of which the vague explanations given to date should be for the most part rejected.*

69. Fig. 30 is the electrocardiogram of a patient with bigeminy clinically, a typical "permanent slow pulse." We found 80 heart beats and a peripheral pulse of 40 per minute. This is a right hand-left foot tracing, at normal speed, with sensitivity one-half normal to keep the image within the plate border.

***No one should think, from these opinions, that I wish to discount the merit of many clinicians studying these same problems by mechanical recording techniques. Since I speak now of the telecardiogram this is not the place to discuss the extensive bibliography on the subject of cardiac innervation and function. I would like, however, to make exception and mention particularly two outstanding studies: *The Study of the Pulse* by James MacKenzie and *Die Arhythmie als Ausdruck* . . . by Professor Wenckebach.**

I would like to express my personal opinion that one has been unable to establish with certainty the nature of extrasystoles with mechanical methods of investigation. In this sense electrical techniques have in a real way allowed us to make a step forward.

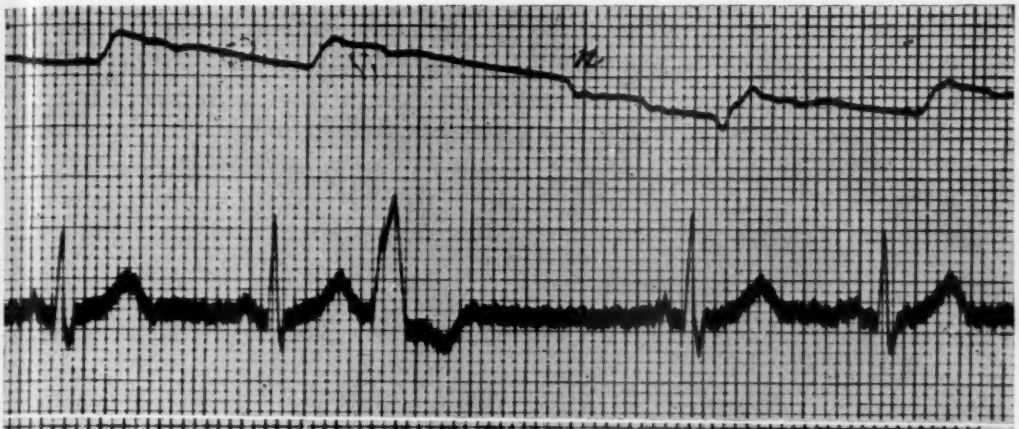

Fig. 27.

Fig. 28.

Fig. 29.

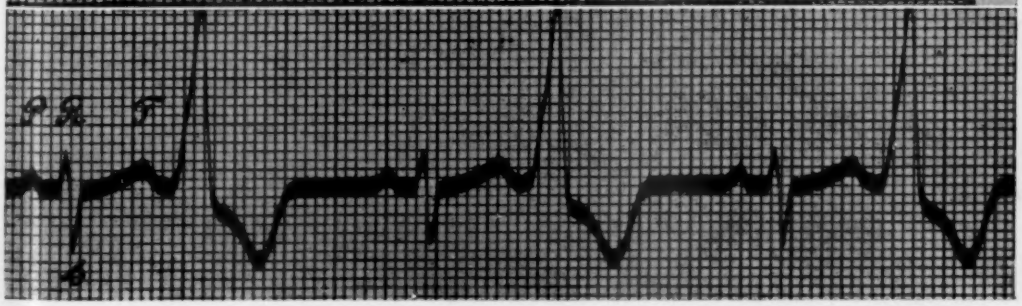

Fig. 30.

Fig. 27.—R. Dropped beat—right hand to left hand.

Fig. 28.—R. Extrasystole without dropped beat—right hand to left hand.

Fig. 29.—R. Atypical beats—right hand to left foot.

Fig. 30.—S. K. Bigeminy—right hand to left foot. 1 mm. along abscissa = 0.04 sec. 1 mm. along ordinate = 2×10^{-4} volts.

70. The normal complexes on this tracing are unremarkable. The P wave is quite distinct, the Q is absent, and the S prominent. After each normal beat there is an immediately occurring extrasystole with upward direction and great amplitude corresponding to 4 millivolts potential difference.*

71. On occasion we observed a series of normal beats, interrupted at intervals by an extrasystole. Another time we found three successive extrasystoles, absolutely identical. While again, we were able to discern two different types of atypical beat.

72. I am afraid of going into excessive detail with further consideration of these phenomena. Before going on I would like to make two further comments concerning atypical contractions.

73. First, they are much more prevalent than one would suppose. Usually one would not suspect extrasystoles in a patient unless dropped beats were found in the pulse. However, in grossly irregular hearts it is difficult to determine the type of irregularity by palpation and virtually impossible to detect extrasystoles.

74. Thus it may happen that in a patient with an unequal and irregular pulse of 150 one would not think extrasystoles were present, and the galvanometer would indicate the contrary, Fig. 31 giving an example.

75. To conclude this review of telecardiograms I will give consideration to the relationship between auricular and ventricular systole. We know that in most instances this relationship is quite intimate, all ventricular beats being preceded by auricular, and all auricular beats followed by ventricular. It is rather important to measure the interval between auricular and ventricular action.

76. To determine this interval with mechanical recording we must have simultaneous arterial and venous pulses, which often gives difficulty. The electrocardiogram, to the contrary, permits easy and precise measurement. I refer to Fig. 9, a fast speed record, in which 1 mm. along the abscissa represents 0.01 sec. We find an interval of 0.175 sec. from the beginning of auricular to the beginning of ventricular systole, and 0.055 sec. between the end of auricular and beginning of ventricular systole. In Fig. 10, a similar type recording on another subject, the intervals are smaller, 0.13 and 0.035 sec., respectively.

77. According to Mackenzie there is a lag in the relationship between the two parts of the heart when the As-Vs (P-R) interval exceeds 0.2 sec. In this situation certain drugs, such as widely used digitalis, are dangerous. With the electrocardiogram it would be simple to follow step by step the influence of various drugs on this interval. My comments on As-Vs interval measurement are generally applicable to all quantitative investigation of heart function. The system in which our curves are traced greatly facilitates such measurements.

78. With a rapid pulse, auricular systole follows ventricular so closely that the normal rest period disappears. It can even happen that ventricular and auricular systole occur partly at the same time. The action curves of the two parts of the heart are partially superimposed, and there is thus overlapping of

*In the thesis of Dr. Goteling Vinnis, Leyde, 1905, we find the mechanical cardiogram of the same subject. We see in these curves a reduplicated pulse. The second part of the curve is repeated regularly, sometimes with the same amplitude, sometimes smaller than the first part.

beats. When auricular systole is so early that the ventricle is still refractory to stimulation, the regular succession of action of the two parts of the heart is disturbed.

79. These considerations are confirmed in Figs. 31 and 32, the latter from a patient with dextrocardia produced by left-sided pleural exudate. The pulse

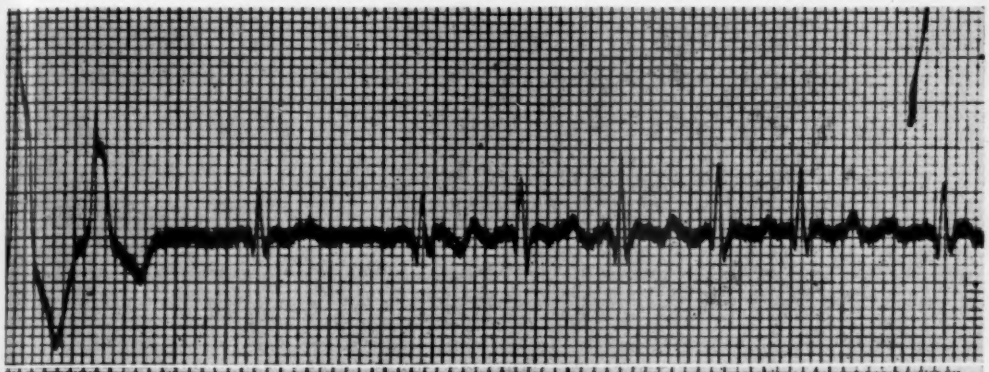

Fig. 31.

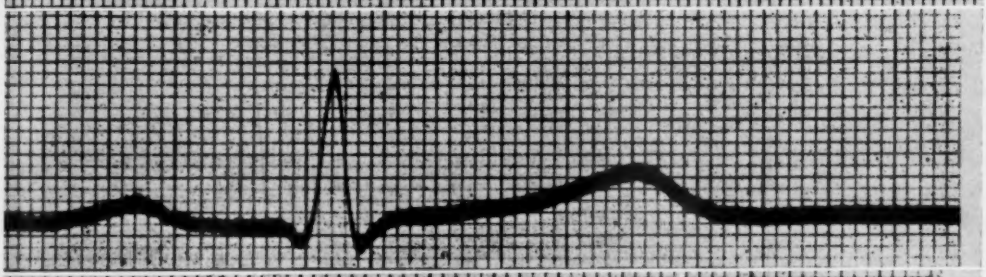

Fig. 9.

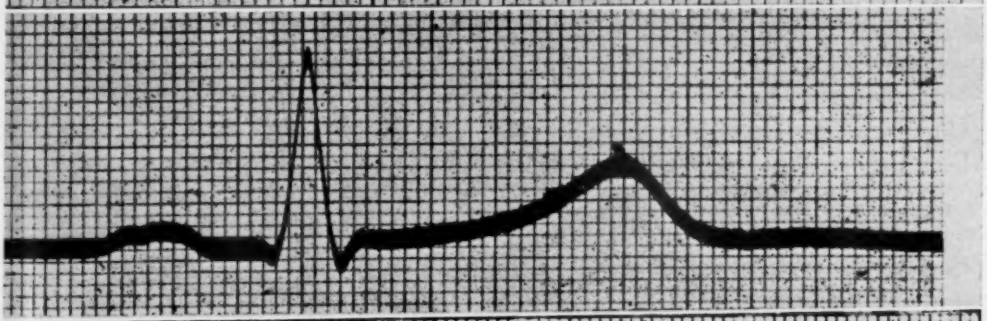

Fig. 10.

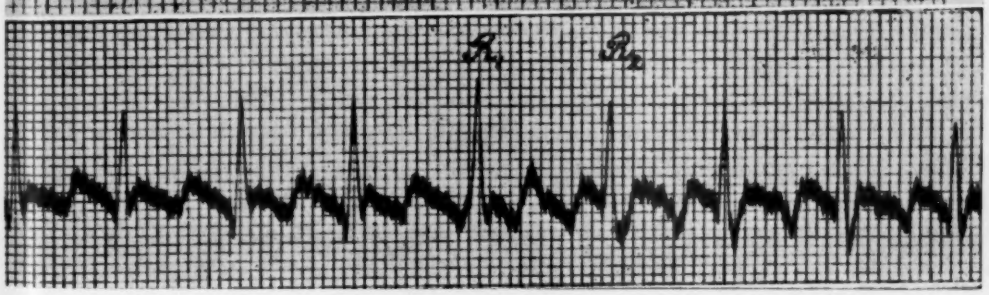

Fig. 32.

Fig. 31.—H. V. W Irregular, unequal pulse. Left hand to left foot.
Fig. 9.—M. Normal. Right hand to left foot. 1 mm. along abscissa = 0.01 sec.
Fig. 10.—Th. Normal. Right hand to left foot. 1 mm. along abscissa = 0.01 sec.
Fig. 32.—L. Dextrocardia from pleural effusion—left hand to left foot.

is rather regular and rapid at 126. The cardiac rest period is completely absent. While elsewhere in the figure one finds two small waves between R waves, note three similar peaks between R_1 and R_2. The middle wave probably represents a nonconducted auricular beat.

80. In Fig. 31 note an analogous instance, and that in both figures the ventricular complexes present all sorts of little irregularities nonexistent in normal hearts.

81. If there is an obstacle to transmission of excitation from one part of the heart to the other, regular succession of action is disturbed, and something besides an auricular beat is needed to produce a ventricular systole (heart block).

82. It may also occur that all rapport between auricular and ventricular function ceases. The two parts of the heart then work independently, each with its own rhythm. This can be induced in mammalian hearts by section of the communicating bundle between auricle and ventricle, the bundle discovered by and named after W. His, Jr. One must take care not to so mutilate the heart that it stops. This experiment, first described by His, has been successfully repeated by other investigators, including Fredericq and Humblet in Liege and Hering in Prague. After section or crushing of the bundle the animal heart displays the remarkable picture of completely independent auricular and ventricular action, termed *allorhythmia*.

83. With the electrocardiogram one can readily visualize the condition of block and allorhythmia. Fig. 33 is the electrocardiogram of a dog under deep chloroform narcosis. The current was conducted from the right anterior extremity to the left posterior, and the tracing is, in general form, analogous to the human electrocardiogram. Auricular waves are marked a_1, a_2, etc. Note that the T wave, upward in most human electrocardiograms, is here directed downward.

84. Between E_1 and E_2 the peripheral end of the vagus nerve was stimulated. Cardiac systole goes on to completion, and an auricular beat a_2 occurs, after which the heart remains quiet until the stimulus is ended.

85. At the end of the excitation an initial auricular beat a_3 appears, not followed by a ventricular beat. At this moment a block exists. Only at a_4 is the block relieved and normal conduction reestablished.

86. With deeper anesthesia and stronger vagal stimulation heart block is accentuated. Fig. 34 is a similarly made record on another dog. After a long vagal induced pause several auricular beats in succession appear before the first ventricular beat develops.

87. The auricular oscillations begin after an arrest of 3 seconds, and only the fifth beat is followed by ventricular systole.

88. Figs. 33 and 34 show that P waves are modified by vagal stimulation while there is no difference in the ventricular complexes (Fig. 33) before and after excitation.

89. Fig. 1 of Plate I is the tracing of a third dog in which there is no association between auricular and ventricular systole, an absolute allorhythmia. The auricular peaks indicated by a_1, a_2, etc. occur at regular intervals and some are even associated with ventricular beats. However, though the auricular rate is around 55, the ventricular is about 35 per minute.

90. I plan to treat in more detail on another occasion phenomena produced by vagal stimulation, and the circumstances in which one can cause block and allorhythmia in the dog heart. Now let us return to the human electrocardiogram.

Fig. 33.

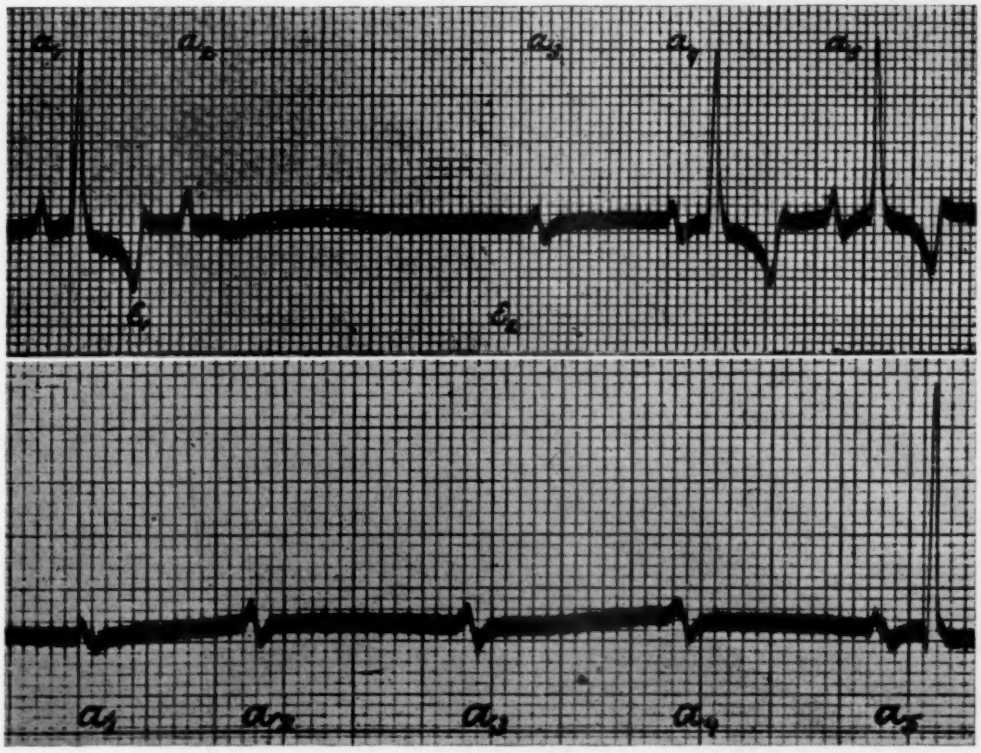

Fig. 34.

Fig. 33.—Dog. Heart block from vagal stimulation—right anterior to left posterior extremity.
Fig. 34.—Dog. Following 3 second vagal arrest. Right anterior to left posterior extremity.

91. In rare cases one can find complete allorhythmia in human hearts. We have had the opportunity of recording the right hand-left foot telecardiogram in a woman presenting this finding, as shown in Figs. 2 and 3 on the large plate.

92. The patient's pulse was only 29. The auricular rhythm is entirely independent of the ventricular, and there are 10 or 11 auricular beats to every 4 ventricular. Since the latter is not an even fraction of the former, the P waves are unequally distributed among the ventricular complexes.

93. It is generally easy to recognize superposition of auricular and ventricular waves. Thus at a_5 and a_{10} (Fig. 2, Plate I) we see a P wave between S and T, and at a_3 and a_8, P waves along the descending limb of T.

94. In the first and last complexes of Fig. 3 (Plate I) the superpositions are noteworthy, the P exactly coincident with the peak of T, producing a higher and more acute T wave.

95. In the first ventricular complex of the illustration the auricular peak

Fig. 1. Fig. 2. Fig. 3.

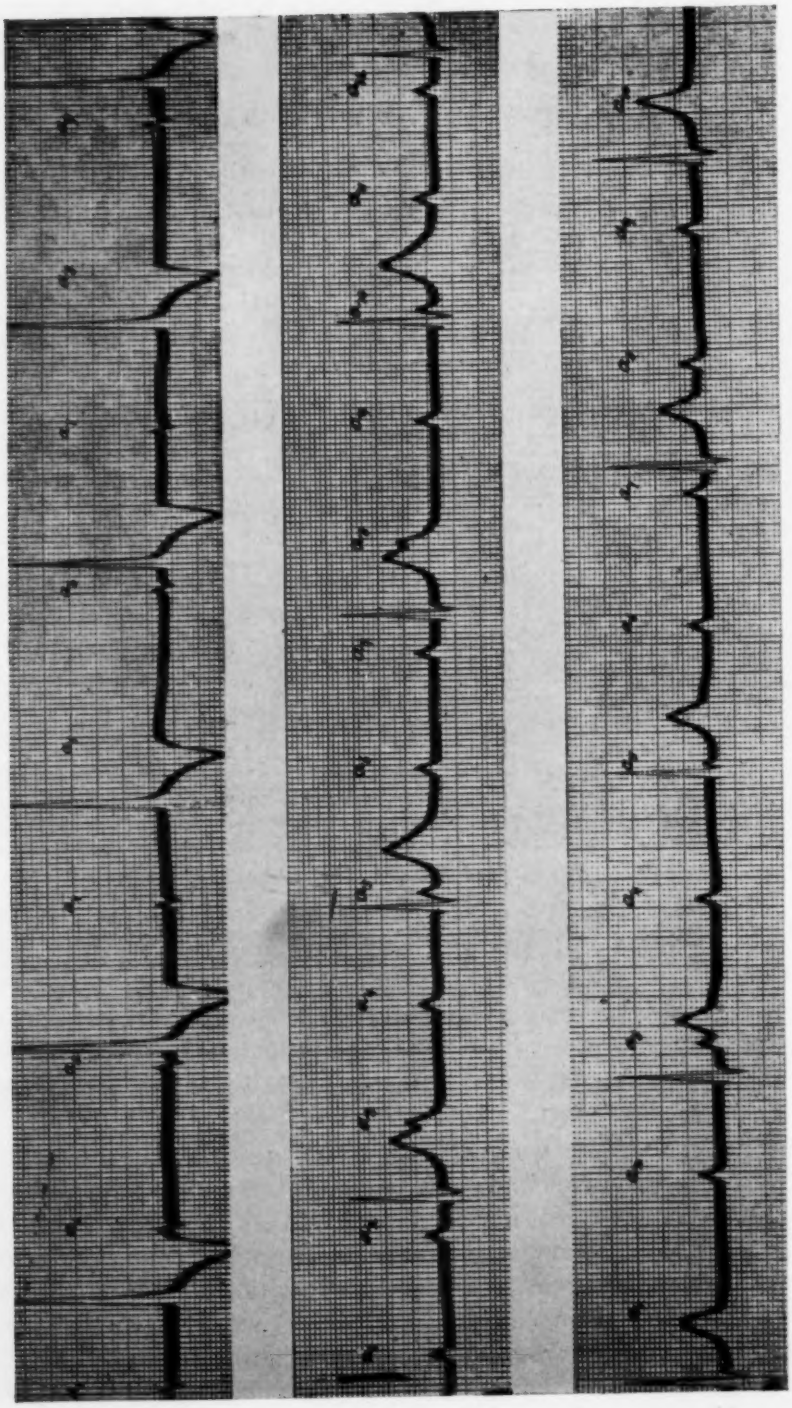

Plate I.—Allorhythmia. Fig. 1, Dog. Fig. 2, S.V.G. Fig. 3, S.V.G.

occurs about 0.04 sec. after the peak of T with a resultant plateau formation rather than a point.

96. It is hardly necessary to say that the telecardiogram makes the certain diagnosis of these abnormalities very easy.

97. Though no atypical beats are seen in these records (Figs. 2, 3, Plate I) I have observed their occurrence in this patient. The abnormality of heart function in this case is thus more complicated than one might believe.

98. In an interesting clinical report published in the "Nederlandsch Tijdschrift voor Geneeskunde", Pel presents a similar case and emphasizes correctly the difficulty in mechanical recording of simultaneous heart motion and venous pulse. However, until now, this method of studying the relation between auricular and ventricular contraction had not been surpassed. Pel states it is " . . . an experiment which requires much time, is fine and delicate work, greatly taxes the patience of the demonstration audience, and gives most uncertain results."

99. In attempting to replace mechanical techniques with roentgen-ray studies, it seems to me that one would not get satisfactory results unless the transitory cardiac movements were recordable as graphic images.

100. Apropos mechanical records Pel says their measurement and analysis give false interpretations. He makes the somewhat imprudent prediction, ". . . that we will never be able to exclude the occurrence of excessively weak ventricular contractions in patients."

101. These problems, outlined vividly by Pel, do not present themselves in recording with telecardiograms. Almost all attempts are successful, quickly performed, and give an absolutely certain result. The method requires no particular skill on the part of the observer and combines precision with application of absolute measurements. While these are the arguments in favor of telecardiograms, we must not disregard the disadvantages.

102. The apparatus requires a special installation and takes up much space. Compared to ordinary cardiographs and sphygmographs it is expensive and complicated. It can only be handled by staff men trained to use it. It may be unreasonable to require of clinical assistants, whose studies are already so heavy, still more difficult technical study.

103. It is thus in the physiology laboratory that these apparati have their place and where this work should be carried out. Where there is this link, actual and figurative, between laboratory and hospital, and collaboration between physiologist and clinician, each remaining master in his territory, there one may fruitfully utilize these new electrical methods of research. I hope I have proved this to you.

104. In conclusion I would like to express my gratitude to Professor Bosscha and the Societé Hollandaise des Sciences for their interest in my research and their support.

105. Others deserving of my appreciation are Professor Nolen and his assistants in the Academic Hospital. Not the least are my faithful aids in the Laboratory of Physiology: K. F. L. Van Der Woerd and H. J. W. Mens, and my ex-assistants H. J. Boeve, W. F. Theunissen, and L. C. de Jongh, whose graduate work has enabled me to present to you this communication on the telecardiogram.

Clinical Reports

TOTAL ANOMALOUS PULMONARY VENOUS DRAINAGE INTO THE PORTAL VEIN

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A REVIEW of the world literature reveals only four well-documented cases of total anomalous pulmonary venous drainage into the portal vein without associated cardiac defects.[1-4] The following description represents the fifth example of this entity.

CASE REPORT

M. H., a 21-day-old white female infant, was admitted to The Mount Sinai Hospital on Sept. 27, 1955 in congestive heart failure.

No abnormalities had been recorded at birth. Three days later, prior to discharge from hospital, the liver was palpable one and one-half fingerbreadths below the right costal margin.

During the 18 days prior to the final admission, the child was noted to have been cyanotic on several occasions during vigorous crying spells. Pallor was present between these cyanotic episodes. The respiratory rate was rapid with grunting inspiration. Feedings were well tolerated. Hospitalization was advised after a routine examination on the day of admission.

Upon entry to the hospital, the patient was found to be a "well-developed, fairly well-nourished" white infant who appeared irritable and tachypneic. There was cyanosis of the fingers, toes, lips, and mucous membranes. The pulse rate was about 200 per minute and the respiratory rate 100 per minute. Body temperature was 99° F. The lungs were clear to percussion and auscultation. The heart rate was 200 per minute and regular. The sounds were of normal quality and intensity. A Grade 2 systolic murmur was heard over the entire precordium, but there was no palpable thrill. The heart appeared somewhat enlarged to percussion. The abdomen was soft and nontender, and the liver was palpable three fingerbreadths below the right costal margin. The spleen was not felt. All peripheral pulsations were normal, and there was no clubbing or edema. The remainder of the physical examination was not remarkable. Laboratory data included a hemoglobin of 15 Gm. per cent; white blood cell count of 21,600 cubic millimeter with 60 per cent segmented forms present. No target cells were noted. An electro-

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cardiogram taken shortly after admission demonstrated the ventricular rate to be 192 per minute with a pattern of right ventricular preponderance. The latter was characterized by the presence of right axis deviation, tall, delayed R waves in aV_R and V_1 as well as the persistence of S waves across the precordium. A chest x-ray revealed a somewhat increased transverse diameter of the heart which appeared to be due to enlargement of the right ventricle. Pulmonary vascular markings were increased from the root of the right lung into the medial aspect of its lower lobe and base of the upper lobe.

Fig. 1.—Chest organs and liver in situ. Note the enlargement of the right ventricle and pulmonary artery. The liver is enlarged.

Treatment during hospitalization consisted of oxygen, digitalis, and penicillin. Despite this therapy, the patient's condition gradually deteriorated. On Oct. 6, 1955, 9 days after admission, the infant expired.

Post-Mortem Findings.—Gross: The body was that of a 4-week-old white female infant, weighing 3,090 grams and measuring 51 cm. in length. There was no evidence of cyanosis or subcutaneous edema. On opening the chest, each pleural cavity was found to contain about 30 c.c. of serous fluid; an unusual prominence of the right side of the heart and the pulmonary artery was noted (Fig. 1). The right ventricle formed the apex of the heart. The left atrium was smaller than normal and sharply delineated from the hilus of the left lung. The left ventricle was also relatively small. The peritoneal cavity contained a small quantity of serous fluid and the liver was conspicuously enlarged.

Heart: The heart weighed 26 grams and was within normal limits of size. The right atrium was considerably dilated and had a large atrial appendage. The vena cavae and coronary sinus entered the right atrium normally. There was a 1 cm. patency of the foramen ovale, partially covered by a septum secundum which bulged toward the left atrium. The tricuspid valve ring measured 4.5 cm. in circumference; the valve was normal. The right ventricle was markedly

Fig. 2.—*A*, Anterior view of lungs showing the pulmonary veins joining in a common trunk which has been resected. The heart is reflected upward, showing the small left atrium. The tip of the pointer is at the foramen ovale. *B*, Posterior aspect of the liver showing the open inferior vena cava. The probe is inserted into the transected unopened subdiaphragmatic portion of the pulmonary vein which enters the portal vein.

hypertrophied, measuring 6 mm. in thickness, 2 mm. more than the left ventricle. Its endocardium was thin and transparent. The pulmonary conus was dilated (Fig. 3), and the pulmonary valve ring was widened, measuring 3.3 cm. in circumference. The main pulmonary artery and its branches were considerably dilated. Its intima appeared grossly normal. The ductus arteriosus was obliterated. The left side of the heart was notably smaller than the right (Fig. 4). The left atrium did not receive any of the pulmonary veins and its auricular appendage was diminutive. The mitral valve ring measured only 3.2 cm. in circumference; the valve was normal

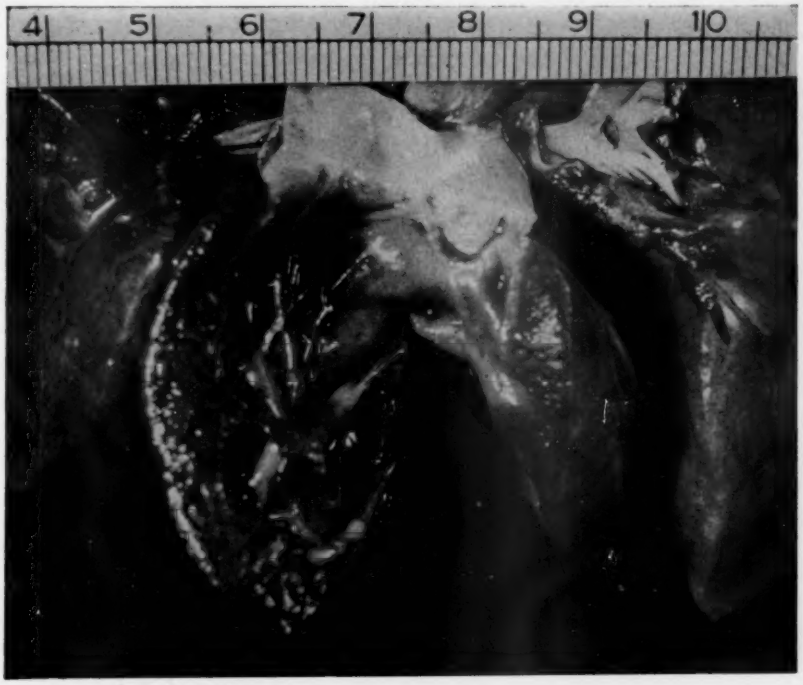

Fig. 3.—Right ventricle. Note hypertrophy of myocardium and dilatation of pulmonary conus and pulmonary artery.

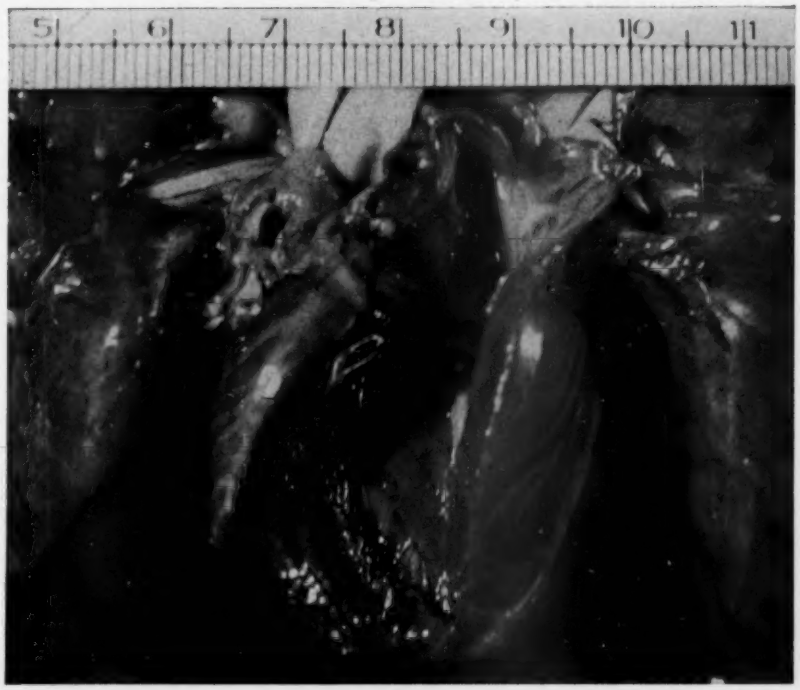

Fig. 4.—Left heart. Note the hypoplasia of the left atrium which has no communication with the pulmonary veins. The left ventricle is relatively small.

though small. The left ventricular wall was 4 mm. thick. The cavity of this chamber was very small and, in addition, a bulging interventricular septum encroached upon it (Fig. 4). The aortic valve ring had a circumference of 1.8 cm. The 3 semilunar valves were normal. The coronary ostia were in the usual position and widely patent. The aorta was moderately hypoplastic.

Lungs: The lungs were voluminous and heavy, weighing twice the normal (120 grams). There was marked congestion and edema, and the vascular tree was strikingly prominent on all cut surfaces. The veins from each lobe converged toward the hilus to form a right and left pulmonary vein which in turn joined in the midline to form a common pulmonary vein. This venous trunk, measuring about 1 cm. in circumference, descended behind the heart, penetrated through the diaphragm to the right of the vena cava and entered the portal vein proximal to the porta hepatis (Figs. 2 and 5).

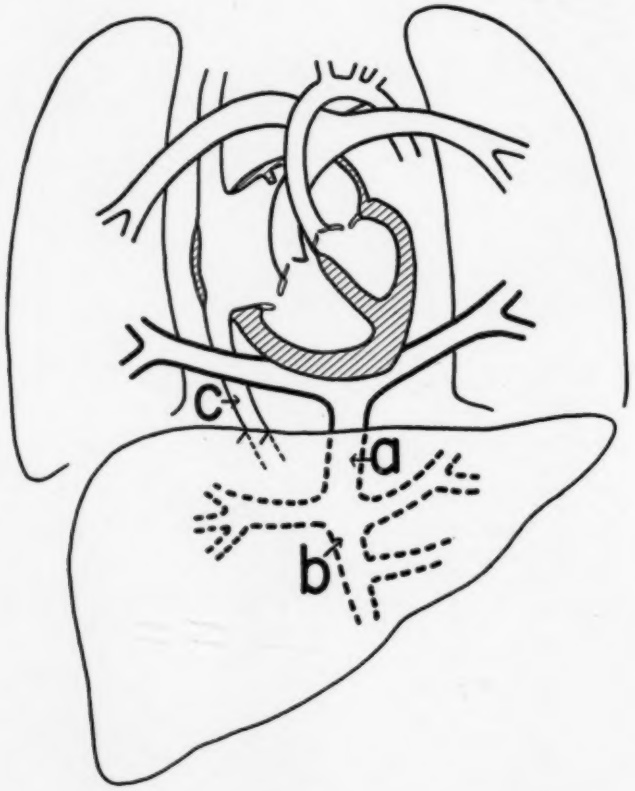

Fig. 5.—Diagram illustrating circulation in total anomalous pulmonary venous drainage into portal vein. *a*, Common pulmonary vein; *b*, portal vein with tributaries and branches; *c*, inferior vena cava.

Liver: The liver was markedly enlarged and weighed 195 grams (normal 127 grams). There was vascular congestion and the major branches of the portal vein, distal to the junction with the pulmonary vein, appeared thickened. The ductus venosus and umbilical vein were obliterated. The hepatic veins drained normally into the inferior vena cava. A solid cord passed between the latter vessel and the common pulmonary vein.

The remaining organs revealed no abnormality.

Microscopic findings: The endocardium and myocardium were normal. There was subintimal proliferation of delicate connective tissue rich in ground substance, in the main pulmonary artery. Patchy intimal proliferation was seen in the common pulmonary vein. The aorta was unremarkable. Cross sections through the ductus arteriosus showed occlusion of the lumen,

both by organized thrombotic material and intimal proliferation. The umbilical vein was obliterated by young, fibroblastic connective tissue, containing a few small vascular channels. There was acute and chronic congestion of the lungs, with numerous mononuclear cells in the air spaces, many of which contained hemosiderin pigment. The elastic arteries in the lung were dilated, while the muscular arteries had narrowed lumina and prominent media and adventitia. There were no intimal changes in any of the intrapulmonic blood vessels. The liver was microscopically normal, except for dilatation of the portal vein branches. Final anatomical diagnosis are as follows: total anomalous drainage of pulmonary veins into the portal vein via a common pulmonary vein; patent foramen ovale; hypoplasia of the left heart and aorta; hypertrophy and dilatation of the right ventricle; dilatation of the pulmonary artery; dilatation and thickening of pulmonary and portal veins; hepatic enlargement and congestion.

DISCUSSION

The first case of total anomalous pulmonary venous drainage was reported by Friedlowsky[5] in 1868. Only sporadic reports appeared in the literature[6-8] until 1942, when Brody[9] described 23 cases of total uncomplicated anomalous pulmonary venous drainage, including 2 of his own. Keith,[3] in 1954, culled from the literature 45 cases of total aberrant pulmonary venous drainage without additional lesions, proved at autopsy, and added 13 authenticated cases observed by him. Gott and associates[4] have recently cited another 20 anatomically proved cases. Most observers[3,9] have found the sites of entrance of the aberrant veins in order of frequency to be the superior vena cava and tributaries, coronary sinus, right atrium, portal vein, and inferior vena cava.

The pulmonary vascular tree arises in a capillary plexus derived from the general splanchnic plexus. This network communicates developmentally with the cardinal or vitelline veins. For this reason, anomalous pulmonary veins always drain into some structure originating from these vessels, to which group the portal vein belongs.[10,11]

The case described illustrates certain clinical features usually produced by this lesion.[3] Except where there coexists a major congenital cardiac anomaly which permits a compensatory shift of circulation from the right side to the left, duration of life rarely exceeds one year. Most cases surviving more than a few days have either a persistent patency of the foramen ovale, the ductus arteriosus, or both. Blood reaches the systemic arteries, therefore, through a communication between the atria and, in some cases, also through the ductus arteriosus. The blood leaving the left ventricle is only partially oxygenated. Cyanosis, however, is generally only minimal[12]; it is aggravated by crying, feeding, and exposure to cold. Terminally, in the presence of congestive failure, cyanosis may become severe. Other clinical symptoms or signs are not well defined. There may be a systolic murmur of moderate intensity over the entire precordium, usually loudest at the left sternal border in the second to fourth interspace. Diastolic murmurs have been reported between the sternum and the apex. Arrhythmias are often present. When the pulmonary veins drain into the left innominate vein, a figure-of-eight pattern or a so-called "mediastinal moustache" may be seen on the chest film.[13] As a rule, x-ray study only reveals evidence of increased pulmonary vascular markings of a nonspecific nature, and right-sided cardiac enlargement. The electrocardiogram shows right ven-

tricular predominance or hypertrophy patterns. The P waves are tall and peaked. These changes reflect the increased load on the right ventricular musculature, right atrium, and pulmonary vascular system. In the case reported above, the essential abnormality consisted of the total anomalous drainage of the pulmonary veins into the portal vein. All the oxygenated blood from the lungs therefore returned to the right side of the heart after traversing the hepatic sinusoids. The condition was rendered compatible with life for a short time by the persistence of a right-to-left shunt via the patent foramen ovale. Whether or not the ductus arteriosus ever represented a route for effective shunt in postnatal life is uncertain, since it had undergone the normal process of obliteration. The relative and absolute increase in size of the right ventricle and the corresponding hypoplasia of the left ventricle are readily explained by the hemodynamics in this anomaly. The dilatation of the pulmonary artery reflects the marked increase in pulmonary blood flow. There is also suggestive evidence of pulmonary hypertension in the early intimal changes in the main pulmonary artery and the microscopic appearance of the small muscular arteries within the lung. This structural characteristic of the muscular arteries, however, is normally seen in fetal life and in the newborn. Its presence a few weeks after birth may not be evidence of increased pulmonary vascular pressure since it may take several months for the adult appearance to develop.[14]

Because of the nonspecific clinical picture presented by this anomaly, based on the pathophysiologic mechanisms mentioned, ancillary means for detection must be employed. Both selective angiocardiography[8,15,16] and cardiac catheterization, employed singly or together, have proved of diagnostic value in this condition. By catheterization, right atrial oxygen saturation may be found to be equal or higher than the peripheral arterial oxygen saturation.[12] This unusual relationship is seen infrequently in other congenital lesions. Furthermore, catheterization study may localize the site of the aberrant communication. An elevation of the oxygen content in the inferior vena cava points toward the portal vein, ductus venosus, or inferior vena cava as the site of abnormal drainage. The procedure is neither difficult nor dangerous even in the very young. Ziegler, in a report of 825 consecutive cases of cardiac catheterization, performed it in 188 infants, ranging in age from 9 days to 1 year. Only 2 to 10 per cent of the patients could not be successfully catheterized. As a result of catheterization, a definite diagnosis previously not made was possible in 75 per cent of the cases studied from birth to 6 months. Thirty per cent of these lesions were found to be operable.

Correct and early diagnosis of total anomalous pulmonary venous drainage may be of more than academic interest. With newer methods of open-heart surgery and hypothermia, the scope of surgical intervention in heart disease is an ever-widening one. Techniques devised by Gerbode,[18,19] have been successfully applied in dogs. These are based on the anastomosis of the anomalous venous trunk to the left atrium. Mueller,[20] in one case, effected partial surgical diversion of a total anomalous pulmonary venous return. The first report of successful complete surgical correction of total aberrant pulmonary venous drainage have recently appeared.[4,21]

SUMMARY

1. The fifth case of total anomalous pulmonary venous drainage into the portal vein to be reported in the literature is presented.
2. Clinical and pathologic data are discussed.
3. The hemodynamics of the lesion are considered.
4. The importance of cardiac catheterization in early diagnosis is stressed.
5. The promise of eventual surgical correction is entertained.

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VENTRICULAR PARASYSTOLE IN A FIVE-YEAR-OLD CHILD

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VENTRICULAR parasystole is a cardiac arrhythmia in which ventricular extrasystoles occur at regular intervals independent of the sinus rhythm, having originated in an automatic center situated in a ventricle. The number of reported cases has not been large[1] but this arrhythmia is easily overlooked as a specific entity and is probably not as unusual as the paucity of reports would indicate.

The following case is presented because the patient is believed to be the youngest reported to have ventricular parasystole.

CASE REPORT

N. D., a white female child, born March, 1951, was first seen at Stanford University Hospital in March, 1955, because of irregular cardiac rhythm and convulsions.

The patient had developed normally and was apparently well until December, 1954, when she had suffered a grand mal seizure during a febrile episode of tonsillitis. She had experienced a second seizure in January, 1955, and a third in February, 1955. A week after the third seizure the attending physician had informed the parents that he noted an irregularity of the heart rhythm and had suggested that the child be sent here for study. The child had had no medications.

On examination, the patient was found to have a blood pressure of 100/70 mm. Hg and a pulse rate of 80. The heart was of normal size, the sounds were of normal quality. A_2 was greater than P_2 and there were no murmurs. An irregularity of the rhythm was noted which disappeared on exercise. The remainder of the physical examination was normal. Routine laboratory examinations were normal and a chest x-ray was reported as showing no evidence of cardiac abnormalities. An electrocardiogram was interpreted as normal except for frequent ventricular premature systoles. An electroencephalogram was interpreted as showing paroxysmal abnormal slow activity, diffuse.

She was seen here for the second time in May, 1956, for further studies regarding her arrhythmia. Her cardiac history and interval history were completely negative and her development had continued to be normal. Physical examination was unchanged from the previous year. An electroencephalogram taken on this admission was interpreted as showing focal spiking in the right parieto-occipital region. Long strips of electrocardiographic record taken during this hospitalization were found to show frequent ventricular premature systoles. On careful examination it was found that these premature systoles were occurring at a regular rhythm with no relationship to the sinus rhythm (Fig. 1). The appearance of occasional fusion beats (Figs. 1 and 2) at the proper time confirmed the presence of two separate foci of activation, one in the sinus node and one in a parasystolic focus in a ventricle.

Mild exercise and carotid sinus pressure did not produce any appreciable effect on the activity of the parasystolic focus or appearance of the record.

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A review of the ECG taken one year earlier showed multiple ventricular premature systoles and although the strips of record are not long enough to be certain of the diagnosis, it probably also represents the same ventricular parasystole.

The child was discharged with a diagnosis of frequent ventricular extrasystoles, from a parasystolic focus, with an otherwise normal cardiovascular system and idiopathic epilepsy.

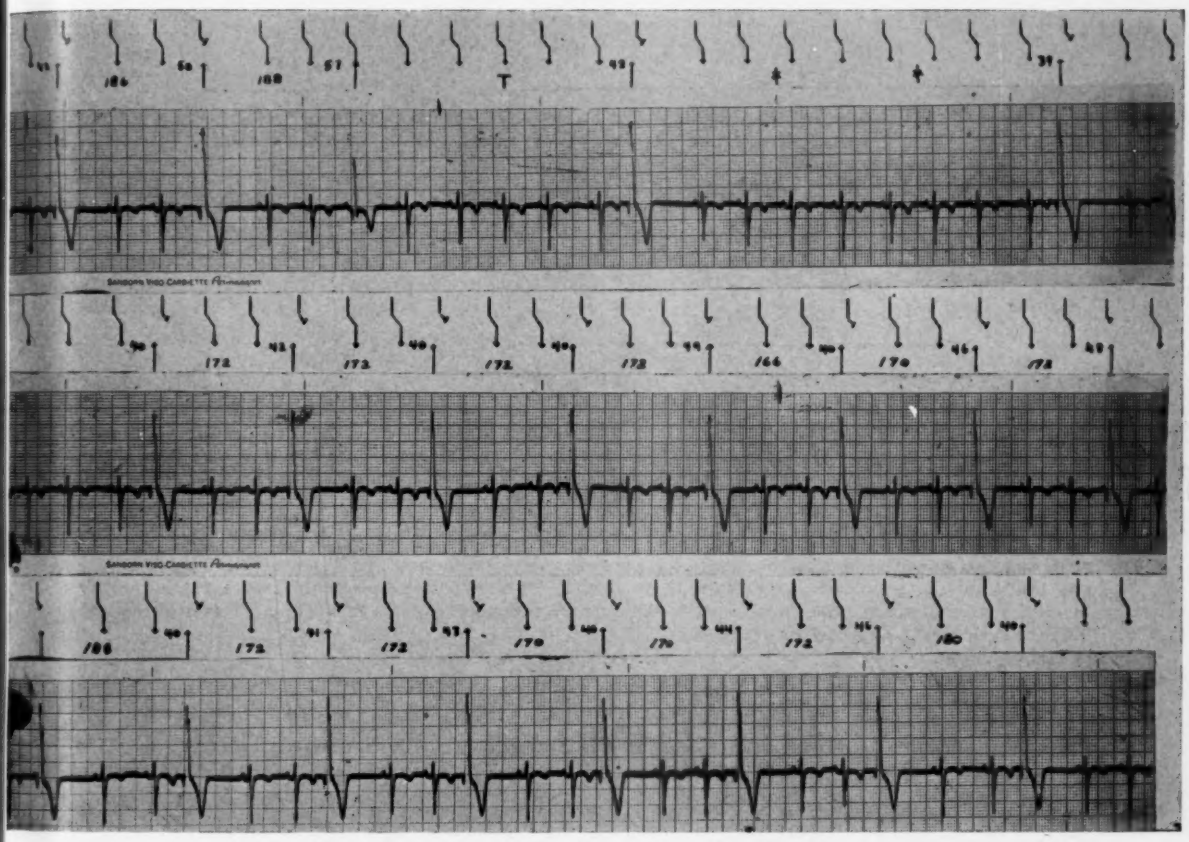

Fig. 1.—Selected strips of electrocardiographic Lead V_1 showing ventricular extrasystoles from a parasystolic focus. The inconstant relationship of the premature ventricular beats to the sinus beats is clearly seen. In the top strip are two intervals without ectopic beats, the first of which is approximately double the usual parasystolic cycle length. This disappearance of the parasystolic complex is due to simple interference. The second period is three times the usual parasystolic cycle length and probably results from an exit block. One fusion beat is seen in the top strip. (Figures above the ECG records are in hundredths of a second.)

COMMENT

The diagnosis of two foci of independent rhythms seems to be established in this instance by the inconstant relationship of the sinus and ectopic beats to each other, by the presence of fusion beats, and by the relatively constant rate of the ectopic rhythm.

A parasystolic focus is usually said to be continuously active with a regular rhythm. Intervals in which the ectopic beats do not appear may result

from interference or from an exit block, an exit block being a phenomenon assumed to be present when interference cannot be demonstrated. In the electrocardiographic record of this case, simple interference and exit block can be demonstrated in prolonged intervals that are multiples of the usual parasystolic cycle length (Fig. 1). There are intervals, however, that are not multiples of the usual parasystolic cycle length (Fig. 2). These intervals might be explained

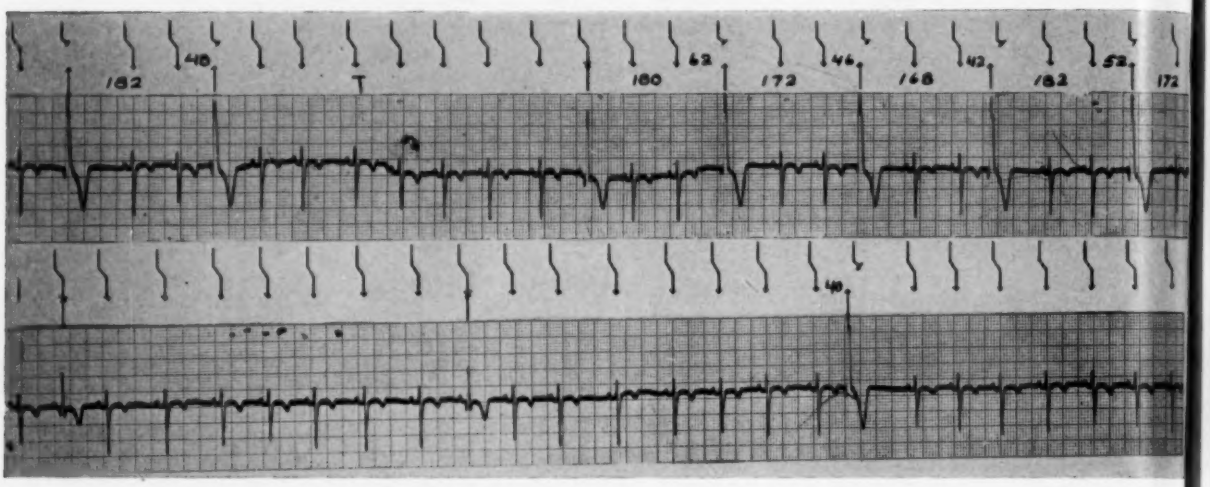

Fig. 2.—A continuous strip of electrocardiographic Lead V_1 showing one fusion beat in the first strip and two in the second. One interval appears in the top strip and two in the second strip that are not multiples of the usual parasystolic cycle length. These periods probably represent temporary inactivity of the parasystolic focus, rather than simple interference or exit block. (Figures above the ECG records are in hundredths of a second.)

as one of the following: (1) simple interference; (2) exit block; (3) brief cessation of activity of the parasystolic focus. Since these intervals are not multiples of the usual parasystolic cycle length, simple interference or exit block cannot be demonstrated. The third possibility, that of brief cessation of activity of the parasystolic focus, must also be considered and it is this possibility that would seem to be the most likely cause for the disappearance of parasystolic complexes in this instance. Two cases of intermittent parasystole of a similar nature have been reported by Scherf and Boyd.[2] It is interesting that fusion beats frequently precede the brief periods of inactivity in this case. The effect of one center upon the other has also been pointed out in cases of intermittent parasystole.[2]

The vast majority of cases of parasystole reported in the English literature appear to be in an age group beyond the third decade and to be associated with some form of cardiovascular disease or abnormality. The youngest case found in the literature is a 12-year-old girl with a normal cardiovascular system.[3] Thus, the appearance of this arrhythmia in a 5-year-old child with a normal cardiovascular system would seem to be quite unusual. It is also of interest that this arrhythmia probably had been present in this child for at least a year prior to its recognition.

SUMMARY

A 5-year-old child with a cardiac pararrhythmia, ventricular parasystole, and a normal cardiovascular system is presented. This is believed to be the youngest such patient reported.

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GIANT P WAVE IN A CASE OF RHEUMATIC HEART DISEASE (ASSOCIATED WITH RHEUMATOID ARTHRITIS)

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THE name "P mitrale" is usually associated more with the abnormal shape of the P wave rather than the abnormal height of this complex. In 1938, Berliner and Master[1] concluded that notching of the P wave was the most constant sign of mitral stenosis in the electrocardiogram and that marked increase in the amplitude and duration of P wave was only found in hearts where both the atria were hypertrophied and, therefore, generally the tricuspid valve was also diseased. Similar findings have been reported by others (Trounce[5]; Thomas and Dejong[4]; and Wood[6]).

The present communication deals with a case of rheumatic heart disease, with mitral stenosis and regurgitation and also aortic incompetence, without any clinical evidence of tricuspid valve disease. During the state of moderate congestive heart failure a P wave of very high amplitude (giant P wave) was recorded in Lead V_1 in this case.

CASE REPORT

K. S., a 25-year-old man, visited the cardiology clinic of this hospital six years ago for the first time with the complaint of painful swelling of various joints of ten years' duration. The polyarthritis started in an acute form, but some pain and swelling persisted in every involved joint. Minor residual deformities of the wrists and knee could be seen distinctly at the time of his first visit. On Sept. 6, 1955, he was admitted in the wards for the third time with signs of moderate congestive failure.

Physical examination showed mild central cyanosis and slight peripheral edema. Neck veins were moderately full. Arterial pulsation in the neck was quite prominent, but there was no abnormal venous pulsation. The pulse was regular, fairly full in volume, with a rate of 96. Blood pressure was 146/65 mm. Hg. He showed the classical signs of mitral stenosis and regurgitation with aortic regurgitation and signs of congestive failure. No hepatic pulsation, however, was palpable.

Laboratory Investigations.—A complete hemogram did not reveal any abnormality. Basal sedimentation rate was 26 mm. first hour (Westergren). Blood urea was 42 mg. per cent.

Posteroanterior, right anterior oblique, and left anterior oblique roentgenograms of the heart are shown in Figs. 1, 2, and 3.

The electrocardiographic findings are seen in Fig. 4.

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DISCUSSION

The first electrocardiogram of this case taken when the patient had signs of moderate congestive heart failure showed a biphasic P wave in Lead V_1 of very high amplitude (10.0 mm.). Such a finding was observed in this case in the absence of any clinical evidence of a tricuspid valve lesion or pulmonary

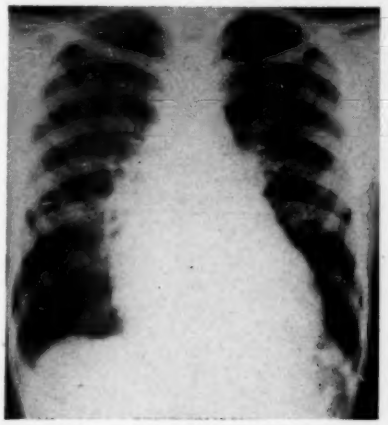

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Anteroposterior view of the heart showing enlargement of cardiac shadow and prominent pulmonary conus. Right costophrenic sinus shows evidence of pleural thickening.

Fig. 2.—Right anterior oblique view showing impression of the enlarged left atrium on the barium-filled esophagus.

Fig. 3.—Left anterior oblique view showing evidence suggestive of some left ventricular enlargement.

infarction or acute pulmonary edema. It is very rare to record a P wave of such a height in a case of mitral stenosis. In our clinic where at least 3,000 graphs are taken every year, we encountered a P wave of such magnitude for

the first time in nine years. While going through the literature we failed to find any definite example of a P wave of such high voltage.

Trounce[5] studied the electrocardiographic patterns in cases of mitral stenosis with a direct-writing apparatus and noted that although the amplitude

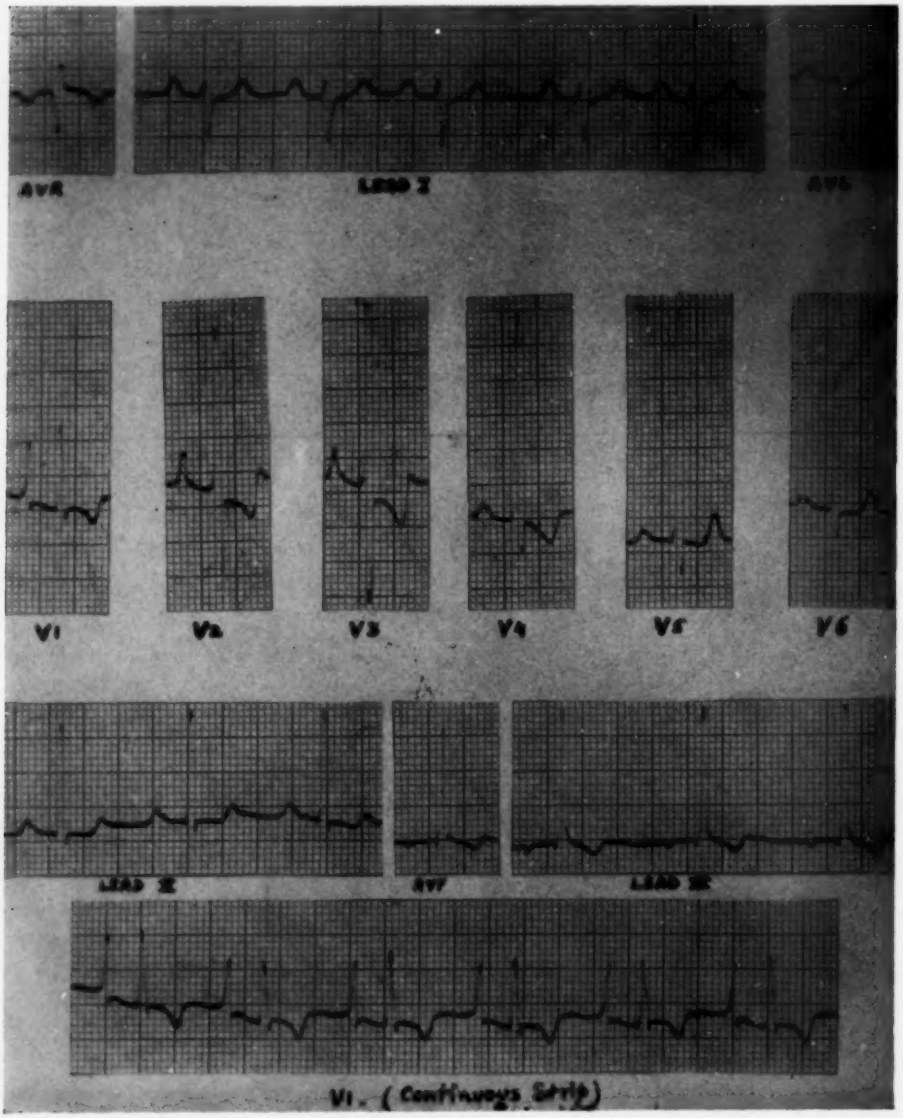

Fig. 4.—ECG showing "P mitrale" in standard limb leads and a "giant P wave" in V_1. There is evidence of sinus arrhythmia and right ventricular strain, and biventricular hypertrophy.

and duration of most of the biphasic P waves in Lead V_1 lay within the normal limits, there was a small group which were outside this range. From a study of his table for the P wave it seems that the highest P wave recorded by him in V_1 was 7 mm. and was probably diphasic in shape.

Leatham,[3] while comparing CR and V leads, noticed that CR leads gave a higher amplitude of P wave and a higher incidence of bifid waves. Thomas and Dejong[4] agreed with these observations and used CR leads for the study of abnormal P waves. They found that the maximum height of P wave in mitral stenosis in their series was 8.0 mm. They used a photographic unit for these investigations. They, however, suggested that if P wave in CR_1 is tall, whether pointed or diphasic, then the right atrium is also under strain or enlarged. According to Goldberger,[2] a very large P wave in V_1 is seen in right auricular hypertrophy and suggests a tricuspid valve lesion in a case of rheumatic heart disease. The example that he gives of a very large P wave in V_1 shows a P wave of not more than 8.0 mm.

We recorded this "giant P wave" in a case of mitral stenosis without any clinical tricuspid valve lesion using V leads and a direct-writing apparatus. It will not be wrong to conclude under these circumstances that the height of this P wave is very unusual, though some enlargement of the right auricle due to frequent history of right-sided failure cannot be ruled out entirely in this case.

SUMMARY

1. A case of rheumatic heart disease with mitral stenosis showing "giant P wave" in V_1 is recorded.

2. The rarity of such a finding in the absence of tricuspid lesion or causes of acute right heart strain like pulmonary infarction and pulmonary edema is stressed.

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WEGENER'S GRANULOMATOSIS

Report of a Case

Howard Levine, M.D.,* and Thomas J. Madden, M.D.**

New Britain, Conn.

THE following case illustrates an unusual type of fulminating vascular disease. In spite of a characteristic clinical picture, it may be difficult to diagnose. It does not respond to current therapy.

CASE REPORT

A 28-year-old machinist entered the New Britain General Hospital on May 7, 1954, with acute respiratory distress and severe midscapular pain. He was in good health until six weeks prior to admission when he noted swelling of the left cheek and deafness of the left ear. At that time Aureomycin, achromycin, terramycin, penicillin, streptomycin, and sulfadiazine were given without improvement. Four and one-half weeks before the present admission a Caldwell-Luc operation was done at this hospital. Following the operation, the patient had a continuous nasal discharge and persistent deafness. One week before his final admission he was awakened from sleep by severe pain in the posterior neck, both shoulders, and the midscapular region. The pain was made worse by deep breathing and recumbency. It recurred several times daily and became constant two days before admission to the hospital. During this time he also had marked shortness of breath, bloating, and abdominal distention. He had slight fever, but no chills.

The patient had had rheumatic fever at the age of 6 years. He had been inducted into the United States Navy without any limitation of activity. While in the Service in 1945, he had had infectious hepatitis.

Physical examination revealed an acutely ill man, sitting up in bed, perspiring profusely, respiratory rate 40 per minute, neck veins full, rectal temperature 103° F. The left cheek was swollen. There was a sanguineous discharge from the left nostril. The anterior portion of the nasal septum was perforated. The left eardrum was reddened and the normal markings were not visible. Heart dullness was percussed in the fifth intercostal space 2.5 cm. to the right of the sternum and at the anterior axillary line on the left. Heart sounds were of poor quality; M_1 was not accentuated; A_2 was greater than P_2. A Grade 2 systolic murmur was heard at the apex. The heart rate was 140, rhythm regular. Blood pressure was 106/70 mm. Hg. There was an area of dullness at the left lung base to the left of the spine. Bronchial breathing was heard at the upper border of this area. Moist râles were heard at the right lung base. The liver edge was 3 cm. below the right costal margin and was tender. Rectal examination was negative.

On admission the patient was given morphine sulfate, ¼ grain, oxygen, a low-salt diet, and terramycin, 250 mg. every four hours. Cedilanid, 0.8 mg., was given intravenously and the

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dose was repeated in four hours. He was maintained on digitalis, 0.1 Gm. daily. Venous pressure was 14 cm. of water; circulation time with Decholin was 14 seconds. Fluoroscopy and x-ray of the heart showed a greatly enlarged cardiac silhouette. Chest films showed a slightly broader superior mediastinal shadow in the recumbent position than in the erect position, suggestive of slight pericardial effusion.

The hemoglobin was 9.5 Gm. per 100 c.c. The red cell count was 4.1 million. The white cell count was 18,550 with 81 per cent segmented neutrophils, 11 per cent nonsegmented neutrophils, 1 per cent eosinophils, 3 per cent lymphocytes, 4 per cent monocytes. The urine specific gravity was 1.012. Tests for albumin and sugar were negative. The sediment contained 2 to 3 red blood cells and 4 to 6 white blood cells per high-power field. Subsequent examinations of the urine showed a 1 plus to 3 plus test for albumin and 10 to 25 red cells and 15 to 20 white cells per high-power field. The sedimentation rate (Westergren) was 117 mm. per hour. The nonprotein nitrogen was 28 mg. per 100 c.c. Serologic test for syphilis was negative. The eosinophil count was 280 per cubic millimeter. Two blood cultures were negative, and one grew *Staphylococcus albus*. Nose culture and throat cultures were negative for pathogenic organisms including *Corynebacterium diphtheriae*. Nasal secretions inoculated into a guinea pig were subsequently reported as negative. PPD skin test was negative in first and second strengths. The cephalin flocculation test was negative. Electrocardiograms showed T-wave inversion in Leads I, II, aV_F, V_3-V_6, interpreted as being due to pericarditis. Antistreptolysin titer was 125 units.

On the third hospital day a loud grating friction rub developed in the posterior midchest. The patient was given 250 c.c. of red cell residue. He remained acutely ill out of proportion to his temperature which varied between 100° and 101° F. His left nostril and left eardrum remained unchanged. On the seventh hospital day, terramycin was discontinued and salicylates were substituted. He developed a severe stomatitis. His urinary output decreased. His urine showed 4 plus albumin and the sediment contained 75 to 100 red blood cells per high-power field. The nonprotein nitrogen rose to 88 mg. per 100 c.c. L.E. cell preparation of peripheral blood was negative. On the thirteenth hospital day the patient had minor clonic convulsions. On that day the serum sodium was 128 meq. per liter, potassium 9.4 meq. per liter, and phosphorus 6.6 meq. per liter. He received intravenous glucose, insulin, and calcium. His blood pressure ranged about 140/80 mm. Hg. The patient died on the fourteenth hospital day. Clinical diagnoses considered at the time of death were active rheumatic fever with pancarditis and acute glomerulonephritis, or hypersensitivity necrotizing angiitis.

PATHOLOGY

The tissue removed from the maxillary sinus six and one-half weeks before death consisted of ulcerated respiratory mucosa and granulation tissue. There was widespread tissue necrosis and a dense infiltrate of plasma cells, neutrophils, and eosinophils beneath the intact surface epithelium. Some portions showed foci of fibrinoid necrosis surrounded by zones of palisaded epithelioid cells. A group of multinucleated giant cells and several arterioles with fibrotic walls and partially or wholly obliterated lumina were present (Fig. 1).

Autopsy.—Autopsy performed by Dr. R. L. Ozere showed a small amount of necrotic pinkish-tan tissue debris in the left maxillary sinus. There was 300 c.c. of clear fluid in the left pleural space. The heart was enlarged in all dimensions and weighed 610 grams. The myocardium was soft and both ventricles were markedly dilated. The pericardial space was obliterated by organizing fibrinous exudate. The chordae tendineae and free margin of the mitral valve were slightly thickened. The endocardial surface of the left atrium was coated with irregularly shaped, slightly elevated, opaque, yellowish-gray plaques varying from 2 to 5 mm. in diameter. The lungs together weighed 995 grams. Organizing fibrinous exudate covered the pleural surfaces of all lobes. The lower lobe of the right lung was partially collapsed and markedly congested. There were grayish-pink foci of consolidation in the right middle lobe. The bronchial and tracheal mucosa were congested and coated with light tan purulent exudate. The liver weighed 2,700 grams and was markedly congested. The spleen weighed 310 grams. The pulp was soft, flecked with light yellowish-gray nodules, and honey-combed with multiple abscesses varying up to 4 mm. in diameter, and containing greenish-yellow pus. The left kidney weighed 250 grams, and the right, 300 grams.

The surfaces were smooth. Both kidneys were swollen and congested and multiple petechiae were present in the mucosa of the renal pelves. There was a circumferential erosion of esophageal mucosa in the middle third. The remainder of the organs showed no significant gross changes. The brain was not examined.

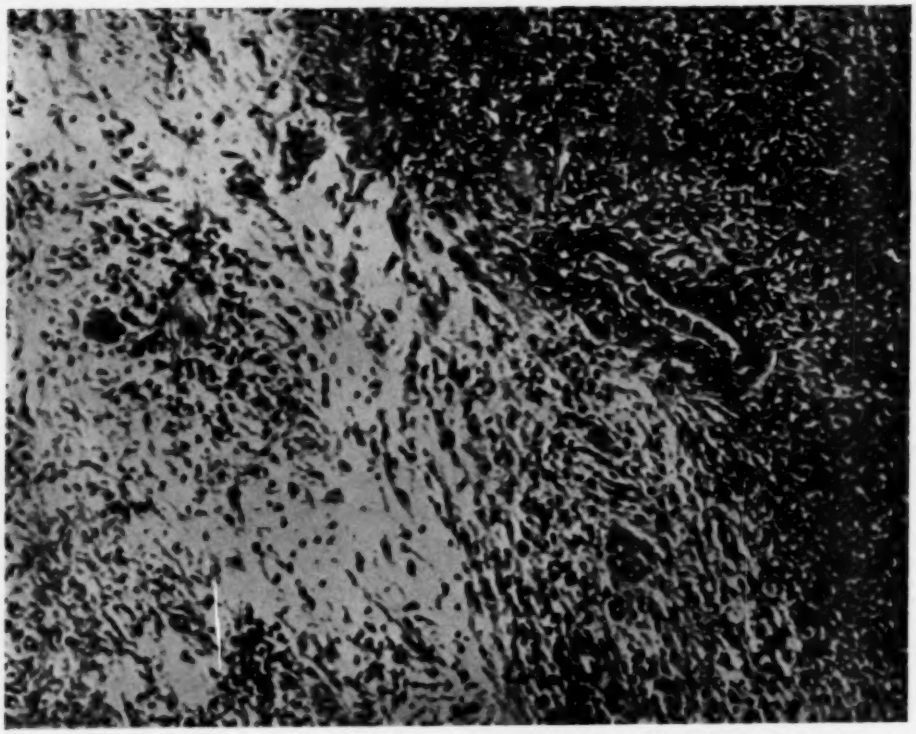

Fig. 1.—Mucosa of maxillary antrum, showing necrosis, granulomatous perivascular infiltrate, and scattered giant cells (×215).

Microscopic Examination.—Acute inflammatory and degenerative changes of the blood vessels were widespread, and marked parenchymal changes were noted in the heart, spleen, and kidneys. Acute panarteritis was found in small arteries of periadrenal fat, a peribronchial lymph node, esophageal submucosa, and subepicardial fat (Fig. 2). The appearance of these vessels was characteristic of so-called "hypersensitivity-type" periarteritis nodosa, and consisted of segmental acute inflammation of the vessel wall and perivascular tissue, accompanied by fibrinoid necrosis, endothelial proliferation, and thrombosis. No giant cells and few eosinophils were present in the inflammatory infiltrate.

The epicardial surface was covered by fibrinous exudate. Subepicardial fat showed marked edema and increased vascularity. Collagen fibrils were swollen and fragmented, and, in some areas, showed slight basophilia. There was an inflammatory infiltrate consisting of neutrophils, eosinophils, plasma cells, and large mononuclear cells in subepicardial fat and in the intermuscular connective tissue septa of the myocardium. The mural and valvular endocardium of the left atrium showed marked focal fibrinoid degeneration of collagen, infiltration of neutrophils, and minute verrucae corresponding to the grossly visible endocardial plaques (Fig. 3). Coronary arteries and veins showed endothelial inflammation similar to that of the endocardium. The lungs were the seat of acute and chronic congestion, focal bronchopneumonia, fibrinous alveolitis, and organizing pleuritis. Acute inflammation of small pulmonary arteries was present in a few areas. The trachea showed fibrinoid change of mucosal connective tissue and focal ulceration.

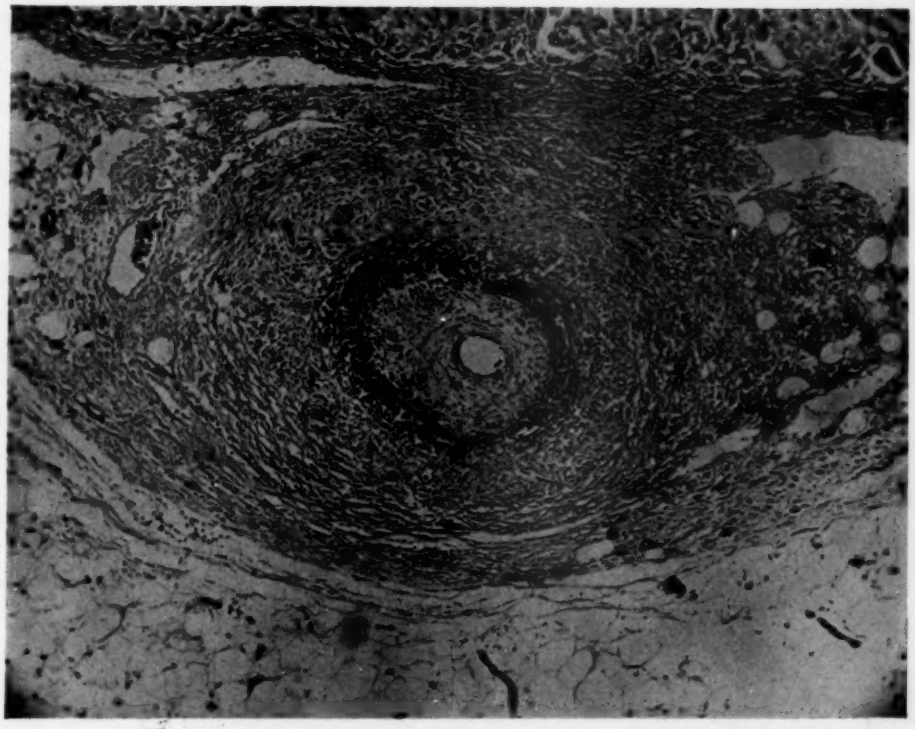

Fig. 2.—Organizing acute panarteritis of periadrenal arteriole (×75).

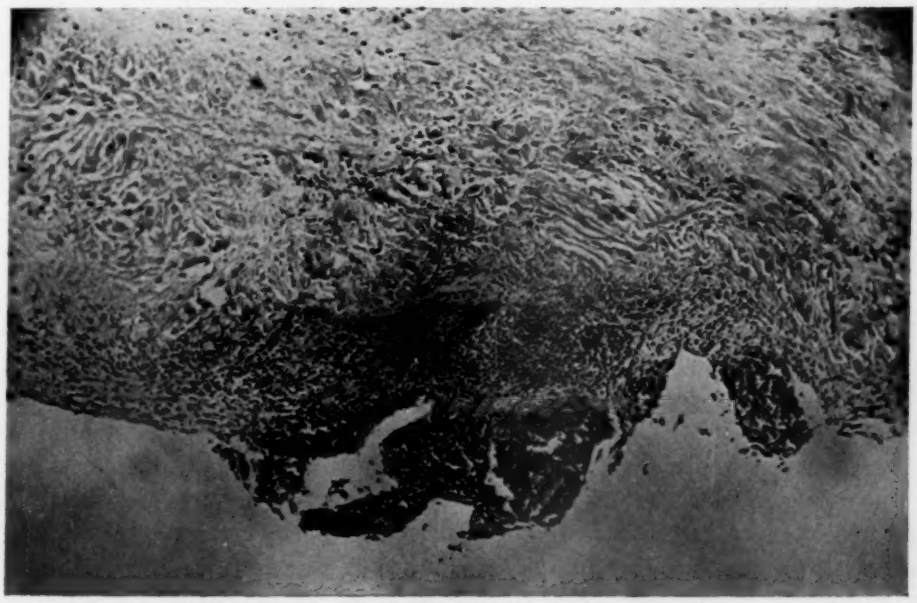

Fig. 3.—Acute mitral valvulitis with fibrinoid change and microscopic vegetations (×75).

There was only slight cellular infiltration, principally of lymphocytes and large mononuclear cells in the tracheal mucosa. The spleen showed acute trabecular arteritis and phlebitis and follicular arteritis with massive necrosis of splenic pulp and formation of miliary abscesses. The kidneys showed marked glomerular changes, involving almost every glomerulus and consisting of focal fibrinoid necrosis of capillary loops, capillary thrombosis, adhesions, epithelial crescents, and polymorphonuclear cell infiltration of the tufts (Fig. 4). In addition, there were interstitial accumulations of neutrophils and large mononuclear cells. The interstitial inflammation was most intense in the periglomerular tissues and in the medullary portion of the kidney. In the latter areas there was focal fibrinoid degeneration of connective tissue.

The anatomical diagnoses were acute necrotizing and granulomatous maxillary sinusitis, left; acute necrotizing angiitis involving coronary, pulmonary, splenic, periadrenal and esophageal vessels; acute pericarditis, myocarditis, and endocarditis; acute necrotizing glomerulitis and interstitial nephritis; acute ulcers of esophagus and trachea; hypertrophy and dilatation of heart; bronchopneumonia, bilateral; chronic passive congestion of viscera.

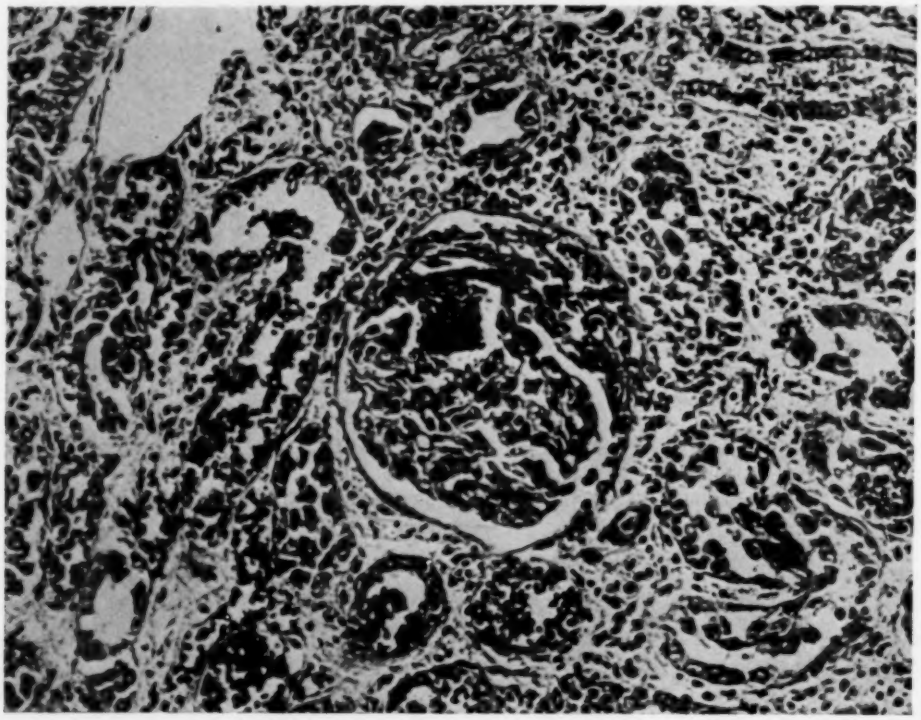

Fig. 4.—Focal fibrinoid necrosis of glomerular tuft, epithelial crescent, and periglomerular inflammation (×245).

DISCUSSION

This patient had the cardinal clinical features of the condition described by Wegener in 1936[1] and 1939.[2] The illness began with severe sinusitis which progressed in spite of a Caldwell-Luc operation and various therapeutic agents, and was followed by a generalized systemic disorder. He had the constitutional symptoms of fever and progressive weakness as well as signs of pulmonary and myocardial damage. Terminally he developed hematuria and albuminuria with increasing renal insufficiency. He died in uremia with a normal blood pressure. He had no abnormal eosinophilia.

The pathologic findings fulfill the anatomic criteria of Godman and Churg[3] for inclusion in the category of Wegener's granulomatosis: (1) necrotizing granulomatous lesions of the respiratory tract, (2) generalized arteritis, and (3) focal glomerulitis. There is a striking similarity of the pathologic findings of this case to those of other so-called collagen diseases or diffuse vascular diseases. The fibrinoid necrosis, endocarditis, and mural and valvular vegetations of the heart are morphologically indistinguishable from the lesions described by Klemperer, Pollack, and Baehr[4] in cases of lupus erythematosus. Many of the vascular lesions are identical with Zeek's[5] "hypersensitivity angiitis." The renal and splenic changes duplicate the findings in cases of sulfonamide sensitivity described by More, McMillan, and Duff.[6] The close morphologic relationship of these various diseases has been discussed in detail by Godman and Churg.[3]

Fahey and associates[7] reviewed 29 cases of this syndrome, assembled from the world literature and from personally observed patients. These authors found the sexes equally affected. Cases occurred in all age groups, but the fourth and fifth decades are most frequently involved. The average duration of the disease is four to seven months and it is usually fatal. ACTH and cortisone seem to have controlled systemic symptoms and inflammatory lesions in one patient included in the series, but this case is atypical because of a prolonged subacute course.

The etiology is thought to be a hypersensitivity state. Wegener[2] postulated a sensitivity to the infecting organism.

Differential diagnosis listed by Fahey and associates[7] includes: (1) specific infectious granulomatous diseases, (2) Boeck's sarcoid, (3) granuloma gangraenescens, (4) allergic granulomatosis, and (5) polyarteritis nodosa.

SUMMARY

A case of Wegener's granulomatosis is presented. This case differs from most previously reported cases in the severity of the cardiac involvement. The similarity of the anatomic changes to those observed in hypersensitivity states, in lupus erythematosus, and in polyarteritis nodosa serves to emphasize the uncertain classification of this condition. We consider it to be a variant of polyarteritis nodosa.

The photomicrographs were prepared by Mr. Peter DeParolis.

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Book Reviews

DISEASES OF THE HEART AND CIRCULATION. By Paul Wood, 2nd Ed., Philadelphia, 1956, J. B. Lippincott Company, 1005 pages.

This book is the British counterpart of Paul White's "Heart Disease," and Friedberg's "Diseases of the Heart" in this country. It is dedicated to Sir John Parkinson. The acknowledgments, in the front of the book, read like a Who's Who of London cardiology. The preface is an extraordinarily well-written epitome of the cardiological advances which have occurred since the first edition of the book (1950), omitting only the advances in knowledge of atherosclerotic processes which, however, are well treated in the text.

The book is a fine standard text; cardiological research is now so closely co-ordinated in Britain and in this country that there is very little bias from what an American reader expects. It will, therefore, be as welcome in an American physician's library as its American counterparts. The scope is about the same, the points of view, and the treatment of the subjects are similar, and it may be fairly stated that it soundly reflects the state and trends of Anglo-Saxon cardiological knowledge at this time.

The book is traditionally arranged. It begins with a description of symptoms and signs of heart disease. Then follows the means of cardiac investigation, with a chapter on electrocardiography (one page to ballistocardiography). There are two general chapters on cardiac arrhythmias and congestive heart failure. The rest of the book is a special part dealing, in succession, with congenital, rheumatic, and other forms of heart disease. (Incidentally, "coronary disease" is here listed as "ischaemic heart disease"—while the cause of the trouble is in the arteries, the functional disturbance arises from dysfunction of the myocardium, so that there appears to be a choice of classification. In common sense, of course, coronary disease *is* heart disease.) Considerable emphasis and space are given to rare forms of heart disease (Chapter XI). In the last pages of the book the author reveals a great insight into the psychic and emotional aspects of cardiology. Considering the great importance which these aspects assume in actually dealing with patients, one must regret that more emphasis has not been given to them in the other sections dealing with treatment.

To a reader who attempts to assess the present state of cardiology, five significant statements may be quoted:

page 264: "The mechanism and even the definition of heart failure have been debated for a century, and are still a source of controversy."

page 471: "There is no evidence as yet that rheumatic fever is caused directly by any infective agent. There is still, perhaps, a remote possibility that a virus is responsible, but the known facts are against it. It is now generally believed that rehumatic fever is an abnormal tissue reaction to the products of hemolytic streptococcal infection in a sensitized individual."

page 766: "There is, as yet, no direct proof that essential hypertension in man is caused by this mechanism" (or any other), and (p. 786) "as yet there is no satisfactory treatment for essential or malignant hypertension."

page 703: "The cause of human atheroma remains unknown." p. 705: "It is believed that it is closely related to disturbances of fat metabolism acting over a long period of time and perhaps also to some alteration in the biophysical properties or biochemical structure of the intima itself."

page 638: "Carditis accompanying toxemia of pregnancy is particularly interesting. That there may be some form of cardiopathy is suggested in certain cases by the behavior of the cardiac output which may fail to rise as expected when the venous pressure is high. On the other hand, the lack of response to digitalis shows that the heart is not overloaded. It is probable, therefore, that in certain instances cardiac function is impaired, owing perhaps to biochemical, rather than to structural changes in the heart muscle."

These are the five crucial problems in cardiology. In every one, ignorance of the basic process is profound, and as one scans the literature on these subjects, only that on atherosclerosis suggests that any worth-while progress has been made in our knowledge in recent years, in spite of the colossal expenditures of time, effort, and money which have been made. It would appear that continued research along the lines which are described in this volume would lead largely to refinement of existing knowledge but not to clarification of the crucial problems. Yet, in the quotations which have been made there are suggestions that some new avenues of research may be available to cardiology, and that perhaps in the biochemical and biophysical laboratories cardiologists may find the answers to the problems which at present block real progress. Is it possible that those who now are studying myocardial and connective tissue cells under the electron microscopes may some day uncover the facts which the cardiologists need? If that be so, it would seem that authors of cardiological texts will then have to shift their emphasis of presentations.

Altogether, the author has the rare gift of being able to cull from an overwhelming literature the important data and to present them in a clear and readable form.

J. J.

DISEASES OF THE HEART. By Charles K. Friedberg, M.D., 2nd Ed., Philadelphia, 1956, W. B. Saunders Company, 1161 pages. Price $18.

This second edition is, as was the first, the most comprehensive single volume text on diseases of the heart in the English language. It should be readily accessible to all physicians whose province includes cardiology, not only for its wealth of information, literally a one-volume encyclopedia, but also for its references which are virtually a bibliography of significant cardiac literature. Although the double-column page has been introduced, it still has been necessary to enlarge the number of pages by over 100. This increase is due to a new chapter on graphic methods and to recent advances stimulated by the present surgical era. Scarcely any significant phase of cardiology has been omitted. Particularly commendable are many of the sections on medical treatment. Nevertheless, the reviewer thinks that the author failed to produce a really great clinical text, which, like a great novel, should create an illusion of reality.

The basis for this last opinion is illustrated, implied, and prophesied by the opening chapter. Thus, the bald statement, "it has been claimed that cardiac tomography may aid in the differential diagnosis between mitral stenosis and mitral insufficiency," is obviously a librarious find and has no operational meaning to the reader. More subtle perhaps is the absence of a discussion of reproducibility which is fundamental to the meaning of difference. For instance, there is a lack of a sense of the difficulty in obtaining reproducible electrokymograms as compared to obtaining reproducible electrocardiograms. A pastiche, partly uncontrolled by personal experience, is unavoidable when a single author covers an entire discipline. But to obtain a live book, the author should explicitly differentiate the knowledge gained by personal contact with patients from the information gained from purely verbal sources.

Equally important is the fact that the book opens with a chapter on graphic methods. This implies and prophesies the author's lack of appreciation of a living person's complaints and the physician's mental and physical responses to these complaints. After all, it is a matter of the questions raised by this interaction which forms the reasons for the use of graphic methods. Thus, cardiac hypertrophy (p. 92) is said to be essentially a postmortem diagnosis and is clinically ignored in the chapter on cardiac enlargement; but hypertension is diagnosed (p. 931) by persistent diastolic hypertension and by the contradictory statement, "evidence of left ventricular hypertrophy (roentgenologic and electrocardiographic)." Actually, left ventricular hypertrophy is diagnosed by inspection and palpation, frequently years before electrocardiographic evidence

of hypertrophy or roentgenologic evidence of cardiac enlargement appear, and certainly before the patient dies. Perhaps for this reason, a section on acute congestive heart failure and constrictive pericarditis without congestive heart failure are nonexistent in this book. The seriatim enumeration of a host of symptoms and signs, each accurate, but frequently diluted with asides on pathogenesis, and frequently not integrated with each other or with the chronologic development of the illness, blights the reader's imagination of reality.

The author has accomplished a Herculean task. His major asset is his ability to gather information from the literature and compress it without loss of clarity or of accuracy into a few pages. For this reason, this book is well-nigh a one volume source book of cardiology. In this sense, it is indispensable.

L. A. S.

Announcements

THE AMERICAN COLLEGE OF CARDIOLOGY will hold its SIXTH ANNUAL MEETING at the Hotel Willard in Washington, D. C., May 15-18, 1957, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N. Y., member of the Publication Committee. The general topic of the meeting will be diagnostic methods in cardiology. The scientific sessions will feature (1) acute and chronic pericarditis; (2) graphic, laboratory, and roentgenologic methods in cardiology, including vectorcardiography, electrocardiography and catheterization; (3) postgraduate symposium on congenital heart disease; and (4) seminar on open-heart surgery. Simon Dack, M.D., New York, will preside with the joint collaboration of Aldo A. Luisada, Chairman, Scientific Program Committee, Division of Cardiology, Chicago Medical School. Various prominent members of the local universities will participate actively in the scientific sessions. There will be numerous scientific exhibits on cardiology and related subjects, organized under Milton S. Saslaw, M.D., Miami, Florida. Dr. Seymour Fiske, New York, is general chairman with Irving Brotman, M.D., Washington, D. C., and George W. Calver, M.D., Trustee of the College, and Physician to the Congress of The United States, in charge of local arrangements. Any further information pertaining to the program may be obtained from Philip Reichert, M.D., Secretary, American College of Cardiology, Empire State Building, New York 1, N. Y.

POSTGRADUATE COURSE IN CARDIOLOGY at St. Francis Hospital and Sanatorium, Roslyn, N. Y., April 15-27, 1957, under the direction of St. Francis Hospital Staff, assisted by outstanding guest speakers. The course is designed to give intensive training in the diagnosis and management of heart disease. The four sections of the course are: (1) Diagnostic techniques in cardiology; (2) Congenital heart disease; (3) Rheumatic fever and rheumatic heart disease; and (4) Degenerative heart disease. Applications to: Rev. Mother Superior, F.M.M., Administrator, St. Francis Hospital and Sanatorium, Roslyn, L. I., N. Y. Registration Fee: $35. for entire course; $10. per section.

CARDIAC AUSCULTATION, a two-day POSTGRADUATE COURSE in practical applied cardiology, has been announced for April 18 and 19, to be presented at the University of Kansas Medical Center, Kansas City, Kansas.

Enrollment for the course is limited to 20 doctors of medicine, with advance enrollment required.

Teaching aids will include for each enrollee an electronic stethoscope, oscilloscope, tape recordings, and phonocardiograms. The registration fee is $50.00.

Further information concerning details of the course, registration, etc., may be obtained by writing the Department of Postgraduate Medicine, University of Kansas School of Medicine, Kansas City 12, Kansas.